STEREOCHEMISTRY

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WITH 87 ILLUSTRATIONS

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PREFACE

OWING to the extent of the field which has been opened up by stereochemical research during the past decade, a full treatment of every branch of the subject was impossible within the compass of the present volume. But since Landolt's book on *The Optical Rotation of Organic Compounds* has been brought nearly up to date and translated into English, there seems no necessity to deal with this division of the subject in such detail as would at one time have been advisable. Moreover, in other fields so much work has been done in recent years that it appeared desirable to treat these investigations more fully than the problems of optical activity. The arrangement of the material, and the space allotted to each section, have been determined by these considerations; while at the same time it is believed that no essential point has been omitted from the following pages.

As it was obviously impracticable to mention every piece of work carried out within the last twenty years, a selection has been made of those cases which appear to throw most light upon the general lines along which research in stereochemistry is advancing at the present day, and the points so chosen have been treated in some detail. As some readers, however, may be interested in general principles only, and not in the details by which the current theories have been supported, it has been deemed expedient in the case of the chapter on Steric Hindrance to devote a section to a summary of the various researches which are described in detail in the other sections. The first and last sections of this chapter together form a connected whole, and the rest of it may be omitted by those

who do not wish to become acquainted with the minutiæ of the research work.

The references given are not intended to be absolutely complete; they are meant to act as guides to the reader, rather than as an index to the literature. In passing, it may be observed that reference in such a subject as this would be greatly facilitated if authors dealing with stereochemical problems would append a sub-title to their main one. At present, many of the papers published are concealed under out-of-the-way names, which does not increase the searcher's chance of finding them.

The abbreviations adopted in the references are the same as those used by the Chemical Society in its *Journal*. It may be pointed out that footnotes in this volume are indicated by means of asterisks; while, in the case of references to the literature, figures are employed. The reader will thus be able to distinguish between a reference and a footnote, without having to interrupt his reading.

It has not been thought advisable to include many tables in the present book, as they would have filled space which could ill be spared; and their presence would hardly have compensated for the loss of a corresponding amount of text. Very complete tables of melting and boiling points are given by Werner in his *Kurzes Lehrbuch der Stereochemie*.

Since the arrangement of atoms in space governs the physiological action of many drugs, it has been necessary to deal with the matter in some detail. In most works on stereochemistry this part of the subject is treated in sections under the heads of the various classes of isomers; but, in the present volume, it seems better to consider the relations between stereochemistry and physiology in a more connected manner and the question has therefore been dealt with in Appendix A.

It may be well to impress on those who are beginning the study of stereochemistry, that the subject is made much more comprehensible if models be used instead of plane formulæ or perspective drawings. In Appendix B, directions are given for the construction of several aids of this description.

In conclusion, my thanks are due to Sir William Ramsay, K.C.B., and Professor Collie, F.R.S., who have read the manuscript; to Mr. F. N. A. Fleischmann, for some notes on one of the chapters; to Mr. F. Sproxton, for criticism of part of the work; and to Mr. W. B. Tuck, for reading the final proofs. I am especially indebted to Dr. J. K. H. Inglis, for suggestions of improvements in the book, and for the criticisms which he has made while reading the proofs. I have also to thank the Chemical Society for permission to use Figures 72–80, which are taken from their *Transactions*.

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The original memoirs of Pasteur, van't Hoff, Le Bel and Wislicenus have been translated into English by G. M. Richardson, and were published in New York under the title, *The Foundations of Stereochemistry.* Pasteur's monograph has also been published as No. 28 of Ostwald's *Klassiker der Exakten Wissenschaften,* and as No. 14 of the Alembic Club's Reprints.

STEREOCHEMISTRY.

INTRODUCTION.

STEREOCHEMISTRY (στερεός, solid) deals with those chemical and physical phenomena which are believed to be caused by the relative positions in space taken up by atoms within a molecule. This arrangement of the atoms is termed the *configuration* of the compound; and just as we can represent the *constitution* of an organic compound by means of its structural formula, so we can represent its configuration by means of its *space formula*. If we have two compounds whose constitutions are identical, while their properties differ in some respects, we conclude that they must differ in configuration, *i.e.* the atoms in the two molecules, though linked to one another in exactly the same way, lie in different positions in space within each molecule; and such compounds, having the same structure but different configurations, we call *stereoisomers*.

It is possible to imagine that the atoms in any molecule may move in one of two ways: they may vibrate as chaotically as the molecules of a substance in the gaseous state; or they may oscillate around certain centres which are approximately stable with regard to each other. As a result of all the research in this branch of chemistry, it is almost certain that the second is the correct view. The atoms in a molecule may be supposed to be in a state of continual vibration, but this vibration merely carries them to and fro about some fixed points, so that at any time two atoms are within a certain distance of one another, and their movements never withdraw them from each other to any appreciable extent. It is therefore most convenient to neglect these atomic motions, and deal with the molecule as if it were a series of atoms whose positions with regard to one another vary only during the course of intramolecular reactions.

The foundation of stereochemistry was laid by Pasteur

during his researches on the tartaric acids in 1861.[1] Twelve years later, Wislicenus[2] called attention to the insufficiency of structural formulæ in certain cases, and pointed out that the only improvement necessary was the extension of plane formulæ into three dimensional ones. In the following year, two independent workers, van't Hoff[3] and Le Bel,[4] published papers in which an explanation was given of the optical activity of certain compounds. Baeyer[5] extended the explanation to some cases of isomerism in cyclic compounds; and since that time the study of the subject has been steadily prosecuted. In 1891, Hantzsch and Werner[6] applied stereochemical ideas to the oxime class of compounds; in 1893, Werner was able to explain certain cases of isomerism in inorganic compounds by means of space relations; and in 1894, Hantzsch[7] put forward a theory of the diazo-compounds which made clear much that had previously been obscure. Smiles[8] isolated in 1900 the first optically active sulphur compound. Later, Pope and his students prepared active compounds of selenium and tin.[9]

We must now consider the possible arrangements in space of the atoms in a molecule MR_4, where M is a quadrivalent atom and the R's are monovalent atoms or radicals.

Chemical evidence has shown that the structural formula of methane is:—

$$\begin{array}{c} H \\ | \\ H—C—H \\ | \\ H \end{array}$$

[1] Pasteur, *Récherches sur la dissymetrie moléculaire des produits organiques naturels.*

[2] Wislicenus, *Annalen*, **167**, 343 (1873).

[3] van't Hoff, *La Chimie dans l'Espace* (1874).

[4] Le Bel, *Bull. Soc. Chim.*, [2] **22**, 377 (1874).

[5] Baeyer, *Ber.*, **18**, 2277 (1885).

[6] Hantzsch and Werner, *Ber.*, **23**, 11 (1890).

[7] Hantzsch, *Ber.*, **27**, 1702 (1894).

[8] Smiles, *Trans.*, **77**, 1174 (1900).

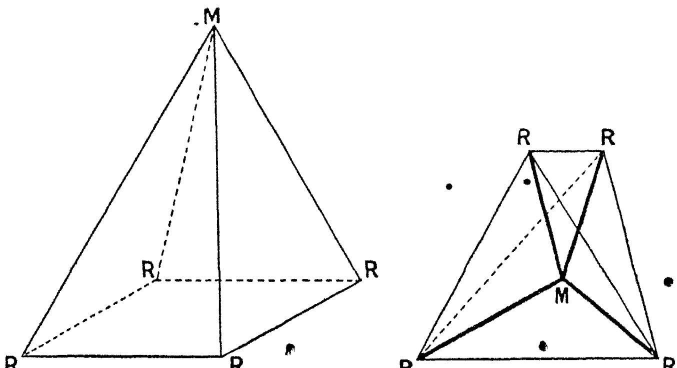
[9] Pope and Neville, *Trans.*, **81**, 1552 (1902); Pope and Peachey, *Proc.*, **16**, 42, 116 (1900).

and from the purely structural point of view such a formula can have but one meaning. It indicates that each hydrogen atom is directly united to the carbon atom. When we attempt to extend this formula into three dimensions, we are forced to consider what positions in space the four hydrogen atoms will occupy, and what relations these positions will have to each other and to the carbon atom. This problem is merely a special case of the general one dealing with the space positions of the groups in the molecule MR_4.

Now in the case of the molecule MR_4, there are two ways in which the atoms R can be arranged: they may all lie in one plane, or they may be so placed that a plane will contain only three of them. On further examination, it will be seen that each of these possibilities contains other two alternatives. In the first case (Fig. 1), the central atom may either lie in the same plane as the other four (I.), or it may lie outside this plane (II.) :—

$$\begin{array}{ccc} & R & \\ & | & \\ R— & M & —R \\ & | & \\ & R & \end{array}$$

(I.)



(II.) (III.)

FIG. 1.

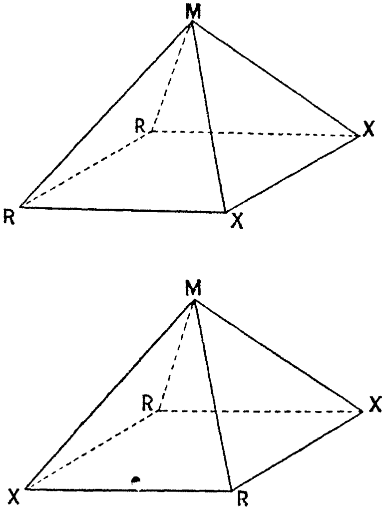
In the second case, there are again two possibilities, for the atoms must be placed at the four corners of a tetrahedron, and this tetrahedron may be either regular or irregular. We need not consider the case of the irregular figure, but will confine our attention to the regular tetrahedron (III.).

We have thus at least three possible space formulæ for the compound MR_4, and it is necessary to find some means by which we can identify the true configuration. This we can do by seeing which formula is capable of yielding the same number of isomers as has been found in practice for the compound in question. It is found that compounds of the type MR_2X_2, *e.g.* CH_2Cl_2; $CH_2(COOH)_2$; $CH_2(NO_2)_2$, exist in one form only, no second isomer having yet been discovered in this class. But if we examine the three types of configuration which we have given above, it will be seen from Fig. 2 that (I.) could give rise to two isomeric compounds; (II.) might also produce two isomers; while (III.) in Fig. 2A is the only one which agrees with practice. It is therefore probable that (III.) is the true configuration of the molecule MR_4.

```
     R
     |
R—M—X
     |
     X

     R
     |
X—M—X
     |
     R
```

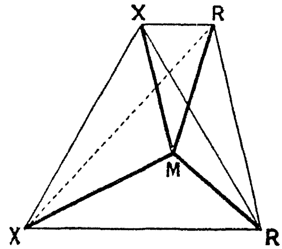
(I.)



(II.)

FIG. 2.

It has been observed that compounds of the type M.*abcd* exist in two isomeric forms, and no other isomers have yet



(III.)

FIG. 2A.

been found in this series. Now configurations (I.) and (II.) each lead to three isomers :—

$$\begin{array}{c} a \\ | \\ b\text{—M—}c \\ | \\ d \end{array} \qquad \begin{array}{c} a \\ | \\ b\text{—M—}d \\ | \\ c \end{array} \qquad \begin{array}{c} a \\ | \\ c\text{—M—}d \\ | \\ b \end{array}$$

The tetrahedral arrangement, on the other hand, yields the correct number of isomers :—

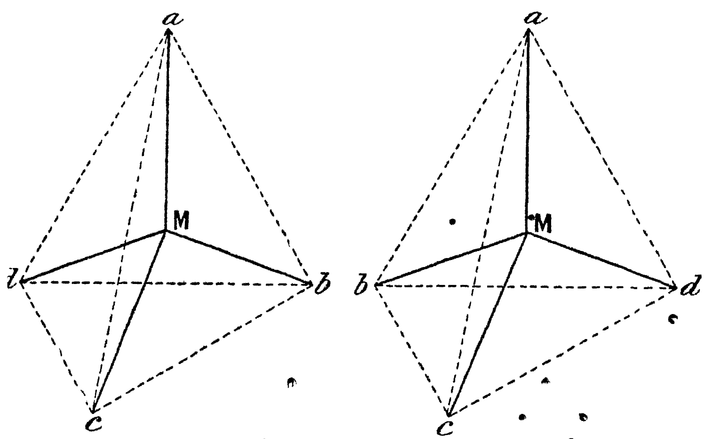


FIG. 3.

It will be noticed that these two arrangements are not superposable upon one another, but are related to one another as an object is related to its mirror image.

We now return to the case of methane. Here we are dealing with the special case in which M is replaced by a carbon atom and R_4 by four hydrogen atoms, so that instead of MR_4 we have CH_4. No change in configuration is likely to result from this series of substitutions, which leaves the molecule in the original symmetrical condition; so methane may be represented by the following space formula (Fig. 4).

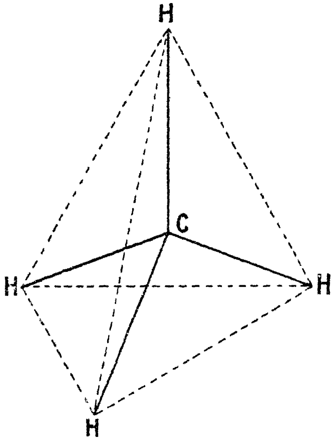
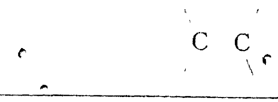


FIG. 4.

Having deduced the configuration of the molecule MR_4, we must now endeavour to find some explanation of the tetrahedral arrangement of the four atoms R.

If we begin with van't Hoff's theory, we find that he treats the carbon atom as a material point from which the four valencies branch out into space toward the corners of the tetrahedron. It has not been definitely stated by van't Hoff that the carbon atom is actually a mere point, but this conception appears to underlie some of his writings. Auwers [1] has shown that, if we accept this view, we are at once plunged into a series of assumptions which cannot be brought into line with our present dynamical ideas. For instance, in the case of the double bond between two carbon atoms, we find that it will be represented by the following:—



[1] Auwers, *Die Entwicklung der Stereochemie*, p. 22 (1890).

That is to say, we are dealing with two forces acting from two points, and these forces, instead of acting along the straight line joining the two points, act through space in such a way as to make an angle with each other. As Lossen has pointed out,[1] this implies that the valencies of the atom, as well as the atom itself, must have a definite position in space. Such forces, however, are inconceivable in accordance with modern views; and, as we cannot bring the idea of the double bond resolving itself into a single line of force into accordance with facts to be dealt with in Section I. of this book, we are forced to reject the van't Hoff conception as insufficient.

Many investigators have endeavoured to explain the origin of the tetrahedral grouping by assuming that the carbon atom is a material body of a certain shape and size. It is not necessary to deal with these views here. Reference may be made to the work of Wunderlich,[2] Auwers,[3] Wislicenus,[4] V. Meyer and Riecke,[5] Naumann,[6] Sachse,[7] Erlenmeyer junior,[8] Vorländer and Mumme,[9] Vorlander,[10] Knorr,[11] Vaubel,[12] Knoevenagel,[13] Bloch,[14] and P. de Heen.[15]

Le Bel[16] put forward the following explanation of the tetrahedral grouping. He assumes that if two atoms come within each other's sphere of attraction, they will approach one another, but that when they come within a certain distance a new repulsive force comes into play which holds them apart;

---

1 Lossen, *Annalen*, **204**, 336 (1880); *Ber*, **20**, 3306 (1887).

2 Wunderlich, *Konfiguration Organischer Molekule* (1886).

3 Auwers, *Die Entwicklung der Stereochemie*, p. 31 (1890).

4 Wislicenus, *Ber.*, **21**, 581 (1888).

5 V. Meyer and Riecke, *Ber.*, **21**, 946 (1888).

6 Naumann, *Ber.*, **23**, 477 (1890).

7 Sachse, *Ber.*, **21**, 2530 (1888); *Zeit. Physikal. Chem.*, **11**, 185 (1893).

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9 Vorlander and Mumme, *Ber.*, **36**, 1470 (1903).

10 Vorlander, *Annalen*, **320**, 99 (1902).

11 Knorr, *Annalen*, **279**, 202 (1894).

12 Vaubel, *Chem. Zeit.*, **21**, 96 (1897).

13 Knoevenagel, *Annalen*, **311**, 194 (1900).

14 Bloch, *Alfred Werner's Theorie der Kohlenstoffatoms* (1903).

15 de Heen, *Bull. Acad. Roy. Belg.*, **1904**, 285.

16 Le Bel, *Bull. Soc. Chim.*, [3] **3**, 788 (1890).

and for the sake of simplicity he makes the further supposition that the range of action of this force may be represented by a sphere. Now, on this hypothesis, the four atoms which are united to the central carbon atom of a carbon compound will tend to approach the central atom until the attractive and repulsive forces acting upon them are equally balanced; and similar effects will be produced by the action of each atom upon its neighbours. Thus all the atoms will be held at distances from each other bounded by their repulsion spheres. If we now assume the repulsion spheres of the atoms to be of such a size that the centres of three of them lie in the angles of a triangle ABC, which is equal to one face of a tetrahedron concentric with the repulsion sphere of the carbon atom, then the centre of the fourth atom will take up the position D and the tetrahedral grouping will be obtained.

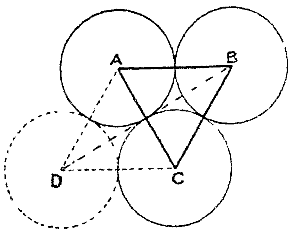


FIG. 5.

Werner[1] has brought forward a theory which, though somewhat difficult to grasp, appears to be the best which has yet been put forward. He makes the simplest assumption of all by supposing that chemical affinity is a force which acts from the centre of any atom towards every point on the surface of a sphere at whose centre the atom lies. Valency, on this view, is an empirical numerical relation, not dependent upon one atom alone, but upon the nature of all the atoms in the molecule. The valency of the carbon atom is reckoned as four, since no compound is known in which one carbon atom is directly united to more than four other atoms. If all atoms be spherical in shape, these four atoms will take up positions in the corners of a tetrahedron circumscribed about the carbon atom, for in this position each will secure a greater exchange of affinity between itself and the central carbon atom than would be possible in any unsymmetrical arrangement.

[1] Werner, *Beitrage zur Theorie der Affinität und Valenz.*

In the following chapters an account will be given of the application of stereochemical views to actual chemical problems; and, where it is necessary, the foregoing theories will be re-examined in the light of the evidence which will then be brought forward.

SECTION I.

STEREOISOMERISM.

PART I.—OPTICAL ACTIVITY.

CHAPTER I.

THE ASYMMETRIC CARBON ATOM.

§ 1.—*GENERAL CHARACTERISTICS OF OPTICALLY ACTIVE COMPOUNDS.*

In a ray of ordinary light the vibrations of the ether take place in all directions in a plane perpendicular to the direction in which the light is transmitted: but when the light is polarized, these vibrations of the ether particles are confined to one plane. In other words, in a ray of ordinary light the vibrations are evenly distributed around the axis of the ray, which is not the case with the light after it has undergone polarization. The plane in which the ray is polarized is called its *plane of polarization*.

We may make the matter clearer by describing certain phenomena which have been observed in the behaviour of tourmaline. Tourmaline is a transparent mineral of a very finely foliated structure. If two thin plates of tourmaline be held parallel to one another, light will pass through them; and by sliding one round on the top of the other, while still keeping them parallel, an increase or decrease in the light passing

through may be produced. It is found, further, that at one point in the revolution no light at all comes through, while the position of greatest illumination is obtained by revolving one of the plates through 90° from the position of total darkness. This is explained in the following manner. If we suppose, merely for the sake of clearness, that the light passes through the spaces between the tourmaline leaves, and is absorbed by the leaves themselves, it will be shown below that the light which emerges from the first tourmaline crystal will be vibrating in planes at right angles to the leaves of the tourmaline plate. The light has, therefore, been polarized by its passage through the tourmaline; and in the emergent ray all vibrations have been stopped except those which the parallel spaces in the tourmaline allowed to pass. If we now introduce into the path of the polarized ray a second tourmaline plate, three positions are possible. We may place it so that its leaves lie parallel to those of the first plate: in which case all the light coming from the first plate will pass directly through the second. Or we may place the leaves of the second plate perpendicularly to those of the first: in which case no light will be able to make its way into the second plate. Or, lastly, we may incline the second plate to the first plate at an angle of less than a right angle. In this case only part of the light will make its way through.

A rough illustration may be given. If the tourmaline plates be represented by two books, the leaves of the books representing the leaves in the tourmaline plate, we may represent the incident ray of light by means of a pencil. It is obvious that we cannot push the pencil through the first book without disturbing the leaves to a considerable extent. But if we could whittle down the pencil into a flat object, it would then pass through easily. Let us pass a paper-cutter into the first book to represent the ray of polarized light. Now, if we bring the leaves of the second book parallel to those of the first one (Fig. 6), we shall find that the paper-cutter will pass through the second book easily; whereas, if we bring the leaves of the second book at right angles to those of the first,

the paper-cutter will refuse to pass into the second book (Fig. 7).

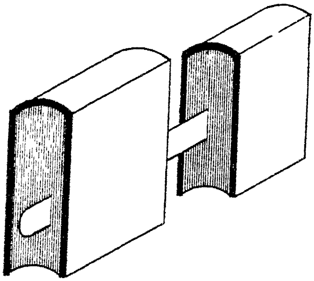


FIG. 6.

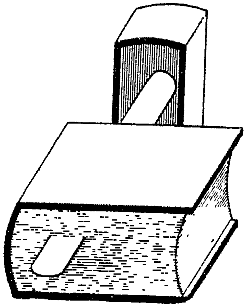


FIG. 7.

It has been found possible to produce waves in the ether of very much greater length than those of light, by causing sparks to pass between the knobs of Leyden jars. These "Hertzian Waves," as they are named from their discoverer Hertz, are also capable of polarization, reflection, etc., like waves of ordinary light; and they are polarized by passage through objects like the leaves of a book, placed as in the diagram. But it has been found that when the leaves of the book are *at right angles* to the plane of vibration of the waves, they are transmitted; if they are *parallel*, currents are produced in each leaf, so that the ethereal impulse is absorbed. And as light waves are believed, and indeed have been shown by Clerk Maxwell, to be qualitatively identical with electric waves, it is certain that light waves pass through tourmaline when the stratification of the mineral is at right angles to their plane of vibration. This explanation does not in any way alter the general result as regards transmission; but it gives the reason why absorption of light takes place, namely, that when absorbed it is transformed into currents which find a closed circuit within the molecule.

It has been found that when a ray of polarized light is passed through certain media, the plane of polarization is turned through a certain angle; and substances which possess this property are termed *optically active*. Arago, in 1811,

observed the phenomenon in the case of quartz; while four years later Biot and Seebeck, by their discovery that certain organic bodies also were capable of rotating the plane of polarization, opened up a new field in chemistry. It soon became possible to divide optically active substances into two classes: those which possess the property only when in the solid condition, and those which retain it even when fused, dissolved or vaporized.

To make this clear, one or two examples may be described. Quartz in the crystalline form is optically active, but if it be dissolved and precipitated as amorphous silica, it has in that state no action upon polarized light. Sodium chlorate, sodium bromate, and ammonium lithium sulphate are all active when crystalline, but lose their activity on being dissolved in water. On the other hand pinene may be dissolved or vaporized without losing its activity.

Thus it would seem probable that in the former cases the action on polarized light is due merely to the crystalline form of the substance, while in the case of pinene it is caused by some peculiarity of the molecular structure of the active body.

This peculiarity in molecular structure was shown by Pasteur

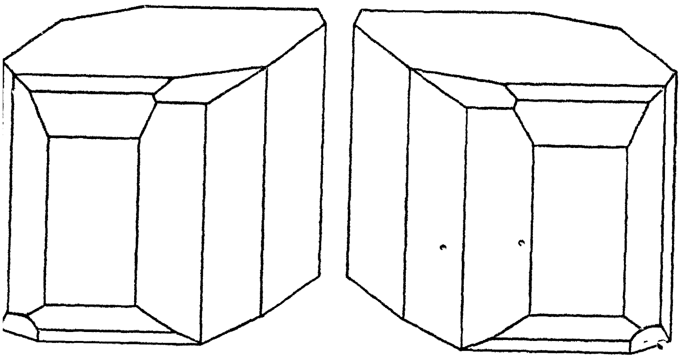


FIG. 8.

to have a connection with the crystalline form of many substances capable of rotating the plane of polarization; in the course of

his work upon the tartaric acids [1] he showed that such bodies crystallize in hemihedral form, and consequently such a crystal and its mirror image would not be superposable on one another. The crystal and another crystal identical with the mirror image of the first would be enantiomorphous. The two figures above show the ends of two crystals of sodium ammonium tartrate (Fig. 8).

Walden [2] states that hemihedrism, though it often accompanies optical activity, is not necessarily exhibited by active substances; but Traube [3] maintains that in the exceptional cases the crystallographic character of the substances has not been determined.

§ II. SPECIFIC AND MOLECULAR ROTATION.

Biot [4] found that the angle of rotation produced in the plane of polarization by the introduction of an active substance into the apparatus was dependent upon three factors :—

1. The wave-length of the light used.
2. The temperature of the substance.
3. The thickness of the layer of substance through which the light was passed.

In order to be able to compare his observations with one another, he reduced them to a common scale, choosing as his standard of *specific rotation* the rotation caused by the substance under examination when one cubic centimetre of liquid contained one gramme of the substance either in the liquid or dissolved condition, and the light was passed through a layer of the liquid one centimetre in length. The light usually chosen is the D line of the spectrum. This specific rotation is usually designated by the symbol $[\alpha]$.

To calculate $[\alpha]$ for a given wave-length of light, at temperature t where l is the length in centimetres of the liquid

---

[1] Pasteur, *Compt. rend.*, **26**, 535 (1848); **27**, 401 (1848); **35**, 180 (1852).
[2] Walden, *Ber.*, **29**, 1692 (1896); **30**, 98 (1897).
[3] Traube, *Ber.*, **29**, 2446 (1896); **30**, 288 (1897).
[4] Biot, *Mem. de l'Acad.*, **2**, 41, 91.

layer, d the weight in grammes of the substance contained in one cubic centimetre, and α the angle of rotation measured in the polarimeter under these conditions, we have :—

$$[\alpha]_{\mathrm{D}}^{t} = \frac{\alpha}{l \, . \, d} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(A)}$$

When the specific rotation is multiplied by the molecular weight of the substance, the product is called the substance's *molecular rotation*. It is customary to use only a hundredth of the actual number, in order to avoid too large numbers. This hundredth part is represented by the symbol [M].

When dealing with solid substances, these formulæ are slightly modified. The solid is, of course, dissolved in some liquid, and the assumption is made that the rotatory power is proportional to the concentration of the solution. We may call this concentration "c," and measure it by the number of grammes of the active substance which are present in 100 c.c. of solution. We should then find that Formula (A) becomes:—

$$[\alpha]_{\mathrm{D}}^{t} = \frac{100 \, . \, \alpha}{l \, . \, c} \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(B)}$$

This formula in turn may be further modified if we consider that the concentration can be found by multiplying together "d," the density of the solution with regard to water at 4° C., and "p" the percentage of active compound by weight in the solution. The new formula would be :—

$$[\alpha]_{\mathrm{D}}^{t} = \frac{100 \, . \, \alpha}{l \, . \, d \, . \, p} \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(C)}$$

Specific rotation, however, is not a constant number, but depends upon several factors—

1. The concentration of the solution.
2. The nature of the solvent.
3. The temperature at which the observation is made.

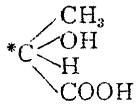
These points will be considered later.*

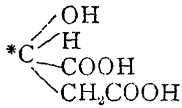
---

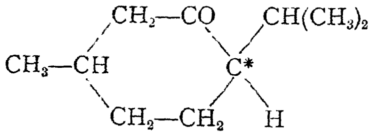
* See Chapter IX of this Part.

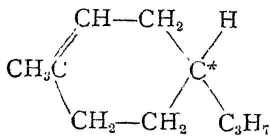
§ III. *THE STRUCTURAL CHARACTER OF THE ASYMMETRIC CARBON ATOM.*

A carbon atom is said to be asymmetric when all the four groups to which it is attached differ from one another either in their chemical or structural nature. For instance, in the following compounds the atom marked with an asterisk is asymmetric :—









Mohr[1] prefers to define an asymmetric carbon atom as one through which no plane of symmetry can be drawn.

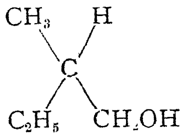
§ IV. *OPTICAL ACTIVITY IN ITS RELATION TO THE ASYMMETRIC CARBON ATOM.*

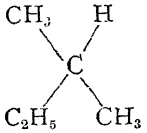
As the result of all research up to the present day, it may be said that wherever optical activity has been detected in a carbon compound, one at least of the carbon atoms * in that compound has been found to be asymmetrical. The very rare exceptions to this rule will be dealt with later. Further (excluding the special cases just mentioned), no case has yet been authenticated, in which a compound known to contain no asymmetric carbon atom has been obtained in an active form. Lastly, if an active body containing an asymmetric carbon atom be so treated that the asymmetry disappears, the activity also

[1] Mohr, *J. pr. Chem.*, [2] **68**, 369 (1903).

* In certain cases asymmetric sulphur, selenium, silicon, nitrogen or tin atoms can replace carbon.

ceases. For example, amyl alcohol with the formula given below, is optically active and contains an asymmetric carbon atom. If the hydroxyl group be replaced by hydrogen, the activity vanishes :—


Active.


Inactive.

Malic acid furnishes an even better example, for here all the four groups attached to the asymmetric carbon can be easily replaced by others. It has been found that mere substitution alone will not destroy the activity unless the asymmetry be also lost. Several active derivatives may be mentioned—bromosuccinic acid, amidosuccinic acid, the esters of malic acid and its amides. When, however, the hydroxyl group is replaced by a hydrogen atom, asymmetry vanishes, and no active substance can be extracted from the resulting compound.

It has been found that each optically active compound has an isomer which, while resembling it closely in most properties, differs from it inasmuch as the effect of the second isomer upon the plane of polarization is equal and opposite to that of the first.

When a compound whose molecule contains only one asymmetric carbon atom, is inactive, it is found that instead of being a simple substance, the body is really a mixture of the two opposite isomers in equal proportions. These inactive compounds are termed *racemic* from the fact that racemic acid was the first of the class to be investigated; and the prefix *r-* is sometimes employed to distinguish them from the active isomers, which are called *dextro-* or *lævo-* * according as they are similar to or different from dextro-tartaric acid in molecular form.

As far as our present knowledge extends, it would seem that the slightest differences in chemical nature between the

* Usually abbreviated to *d-* and *l-* ; the racemic form being distinguished by the prefix *r-*, and the symbol *dl-* being used to indicate a mixture of the two antipodes.

groups attached to the asymmetric carbon atom suffice to produce optical activity. Swarts[1] has shown that bromo-chloro-fluoro-acetic acid :—

$$\begin{array}{l} \mathrm{Br}\diagdown \\ \mathrm{Cl.C.COOH} \\ \mathrm{F}\diagup \end{array}$$

can be obtained in active forms.

§ V. THE NUMBER AND CHARACTER OF ISOMERS CONTAINING ONE OR MORE ASYMMETRIC CARBON ATOMS.

According to the Van't Hoff-Le Bel theory, compounds of the type C.*abcd* with one asymmetric carbon atom may be represented by the following configurations :—

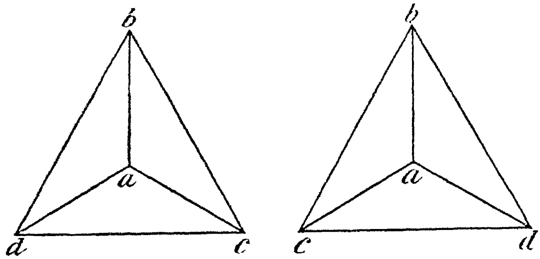


FIG. 9.

In the one case the atoms are arranged in one direction round the base of the tetrahedron representing the carbon atom, in the other they are arranged in the opposite direction. Now let the absolute rotation of the complex group —C*bcd* be called A. Then the two radicals will have rotations of − A and + A.

Passing to the case of a compound with two asymmetric carbon atoms, say *bcd*C—C*efg*, and supposing that the group —C*efg* has a rotatory power of ± B, we find that there is now a possibility of four different isomers which can be represented by :—

[1] Swarts, *Bull. Acad. Roy. Belg.*, [3] **31**, 28 (1896).

1. $+A$ $+B$	2. $+A$ $-B$	3. $-A$ $+B$	4. $-A$ $-B$

Two of these, Nos. 1 and 4, possess equal and opposite rotations, and the same is true for Nos. 2 and 3. Hence equimolecular mixtures of No. 1 with No. 4 and No. 2 with No. 3 will be inactive; though each molecule contains an asymmetric carbon atom.

Dealing in a similar manner with the case where there are three asymmetric carbon atoms in the compound, we find that eight isomers are possible; and if the compound be :—

$$bcdC—C(ef)—Cghk$$

where the rotations of the three complex groups are A, B, and C, we have the following scheme :—

1. $+A$ $+B$ $+C$	2. $+A$ $+B$ $-C$	3. $+A$ $-B$ $+C$	4. $+A$ $-B$ $-C$	5. $-A$ $+B$ $+C$
6. $-A$ $+B$ $-C$	7. $-A$ $-B$ $+C$	8. $-A$ $-B$ $-C$		

Here, as in the last case, a mixture of No. 1 with No. 8 would be optically inactive, as would No. 2 with No. 7, No. 3 with No. 6, and No. 4 with No. 5.

From these examples the reader can work out for himself the relationships between the isomers with four, five, or more asymmetric carbon atoms in the molecule.

So far we have been considering the case of compounds with an asymmetrical structure formula; but now we must deal with molecules of the type *bcd*C—C*bcd*. It is evident that in this case the number of different isomers will not be so great, since some of the configurations will be identical with one another. Recurring to the case of the compound *bcd*C—C*efg*, since the group —*efg* is here replaced by —C*bcd*, the rotation B is also replaced by A. Hence the four formulæ already arrived at for an unsymmetrical chain, become :—

1.	2.	3.	4.
$+A$	$+A$	$-A$	$-A$
$+A$	$-A$	$+A$	$-A$

Here Nos. 2 and 3 are identical and inactive; No. 1 has a rotation equal to twice A, while No. 4 has an equal and opposite rotatory power. It must not be concluded that the form expressed by Nos. 2 and 3 is a racemic form, *i.e.* one which is capable of separation into two other isomers of equal and opposite rotation. Its inactivity is not caused by the mixture of two optical antipodes, but is due to *internal compensation*—one half of the molecule tending to turn the plane of polarization to the right, while the other half-molecule turns it to the left.

The same process for discovering the number of possible isomers can be applied to any compound of the type :—

$$bcd\mathrm{C—C}f_2\mathrm{—C}bcd$$

as it is merely a repetition of the same case. An investigation of the general case gives the following result :—

If n = number of asymmetric carbon atoms in the compound,
N = " possible isomers,
i = " inactive (internally compensated) forms,
a = " active (antipodic) forms,
$r = \frac{a}{2}$ = " racemic forms.

Class I. n even or odd: structural formula not divisible into two halves.

$$N = 2^n;\ a = 2^n;\ i = o$$

Class II. n even: structural formula divisible into two halves.

$$N = 2^{n-1} + 2^{\frac{n}{2}-1};\ a = 2^{n-1};\ i = 2^{\frac{n}{2}-1}$$

Class III. n odd: structural formula divisible into halves if middle carbon atom be excluded.

$$N = 2^{n-1};\ a = 2^{n-1} - 2^{\frac{n-1}{2}};\ i = 2^{\frac{n-1}{2}}$$

§ VI. *PSEUDO-ASYMMETRY.*

Hitherto we have considered compounds of symmetrical structure which contain one, two, four, or any higher *even* number of asymmetric carbon atoms. The case of a compound with three asymmetric carbons differs from those already described, owing to the possible occurrence of a different kind of asymmetry. An example of this class is to be found in compounds of the type *abc*C—C*de*—C*abc*. If an observer could be stationed on the central carbon atom of the chain, he might find by looking to his right hand that the order in which *a*, *b*, and *c* were arranged round the axis of the molecule was the same as that which he saw in the groups about the carbon atom on his left hand. In that case, obviously the central carbon atom would not be asymmetric. But if, on the contrary, he looked to his right and saw the atoms arranged as in Fig. 10; while on the left they were arranged as in Fig. 11, it would be obvious that the carbon atom on which

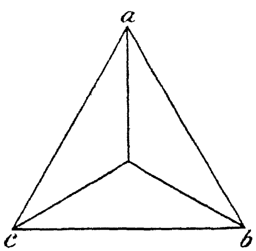


FIG. 10.

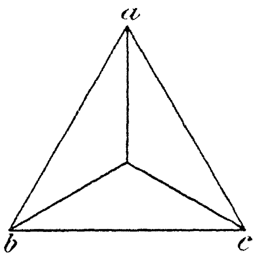


FIG. 11.

he was situated was not symmetrical, although it was joined to two structurally symmetrical groups. Such a case is named *Pseudo-asymmetry*,* and for the sake of clearness we shall indicate the pseudo-asymmetric carbon atom by the symbol Ps, and its activity by Ps + and Ps −.

In the case of the compound *abc*C—C*de*—C*abc*, making the same assumptions as in the previous cases, we have four possible isomers:—

* Pseudo-asymmetry does not necessarily involve optical activity.

$$
\begin{array}{cccc}
1.\ +\mathrm{A} & 2.\ -\mathrm{A} & 3.\ +\mathrm{A} & 4.\ +\mathrm{A} \\
\mathrm{C} & \mathrm{C} & +\mathrm{Ps} & -\mathrm{Ps} \\
+\mathrm{A} & -\mathrm{A} & -\mathrm{A} & -\mathrm{A}
\end{array}
$$

The first two configurations represent two non-superposable mirror-images; and are therefore optical antipodes. The third and fourth types, however, are not mirror-images, nor are they active compounds. They represent a new class of isomers. A further detailed consideration of this subject is at present unnecessary. It will be sufficient to point out that in the case of a compound of the type $abc\mathrm{C}$—$\mathrm{C}d_2$—$\mathrm{C}efg$, when the two groups "*d*" are structurally identical but asymmetrically arranged, there is a possibility of two pseudo-asymmetric isomers and eight others in which pseudo-isomerism is not shown.

§ VII. *THE GRAPHIC REPRESENTATION OF THE CONFIGURATIONS OF SYSTEMS CONTAINING SEVERAL ASYMMETRIC CARBON ATOMS.*

In order to obtain a clear conception of the space relations of compounds containing several asymmetric carbon atoms, it is necessary in most cases to use models. Several of these are described in Appendix B. It is not always possible, however, to have a model at hand, and it is therefore desirable to find some method by which the results obtained by using a model may be transferred to paper. The signs used in the preceding sections are not sufficient, as they give no clue to the actual space arrangements of the atoms.

The configuration formulæ devised by Fischer are usually employed. The method by which they are deduced from the actual model will be understood if we take the case of tartaric acid as an example. The model is built up from tetrahedra in the usual manner, and is then laid upon a sheet of paper in such a way that the four carbon atoms lie in a plane *

* Fischer uses indiarubber models, which can be pressed down until all four carbon atoms lie in a line upon the paper. His method leads to the same result as that described above.

perpendicular to the surface of the paper, while the hydrogen atoms and hydroxyl groups lie *above* the plane of the paper (see Fig. 12). The relative positions of the groups are then projected upon the paper as shown.

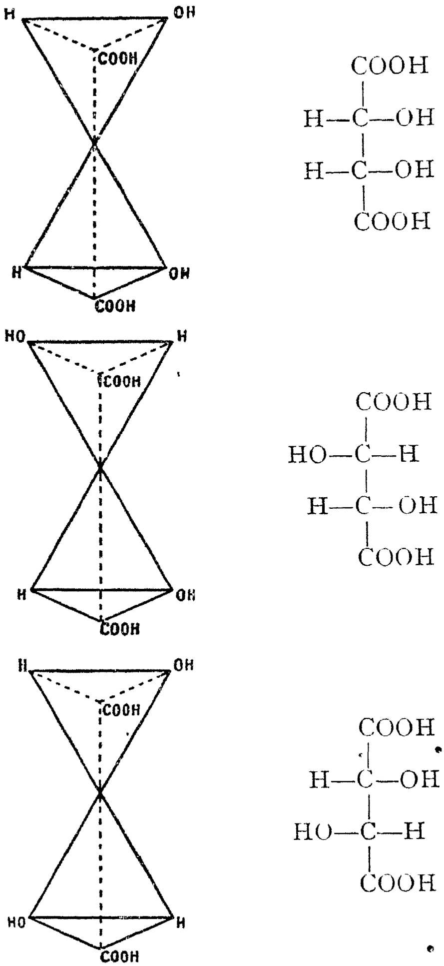


FIG. 12.

Formulæ of this kind enable us to decide at once whether or not a compound with a given configuration is active or inactive. If the model possesses a plane of symmetry—*i.e.* if it can be divided into two halves symmetrically placed with regard to each other—then it represents an inactive compound; while if it has no such plane of symmetry it will be active. For instance, the first of the two following compounds is active, the second inactive:—

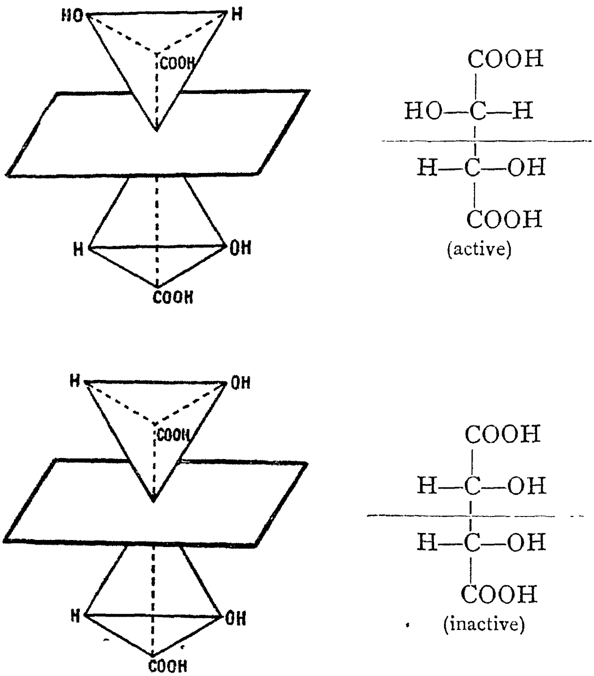


FIG. 13.

Owing to the fact that such a formula, when written in full, occupies a considerable space, Meyer and Jacobson[1] suggest

[1] Meyer and Jacobson, *Lehrbuch der organischen Chemie* (Erste Auflage), i. 904.

that the asymmetric carbon atoms might be left unprinted. With their scheme, the above two formulæ would be written:—

```
        COOH              COOH
    HO– ¦ –H           H– ¦ –OH
     H– ¦ –OH          H– ¦ –OH
        COOH              COOH
```

It is usual to adopt this method, but for the sake of compactness the lines are omitted and the two formulæ written thus:—

```
      COOH          COOH
    HO.H           H.OH
      H.OH         H.OH
      COOH          COOH
```

Even in this form such formulæ would be too clumsy for many purposes, and Fischer[1] has proposed a species of nomenclature which appears more suitable. He uses the signs + and −, not in the sense we have already given them in the preceding sections, but simply to denote whether a substituent lies on the right or the left side of the configuration formula. The formula is to be written so that in the sugars the aldehyde group occupies the top line, while the carboxyl group in the monobasic acids is also placed in that position. The carbonyl group in ketoses is placed in the second line from the top. The counting begins from the top line, and the sign + or − denotes the position of the hydroxyl group. As examples of this we may quote one or two compounds:—

```
       CHO                     CH2OH
     H . OH (+)                 CO
    HO . H  (−)             HO . H  (−)
     H . OH (+)              H . OH (+)
     H . OH (+)              H . OH (+)
      CH2OH                   CH2OH
```

d-Glucose or Hexanpentolal + − + +

d-Fructose or Hexanpentol-2-on − + +

[1] Fischer, *Ber.*, **27**, 3189 (1894).

$$\begin{array}{ll} & \text{COOH} \\ \text{H.OH} & (+) \\ \text{HO.H} & (-) \\ \text{H.OH} & (+) \\ \text{H.OH} & (+) \\ & \text{COOH} \end{array}$$

d-Saccharic acid or
Hexantetroldicarboxylic acid $+ - + +$

Still another system of nomenclature has been put forward by Maquenne.[1] He suggests numbering the carbon atoms in any compound, and writing all the numbers of those asymmetric carbon atoms which have their hydroxyl groups on one side of the configuration formula above a line, while the others are written below; *e.g.* *d*-glucose is:—

$$\begin{array}{cccccccccc} & & \overset{(2)}{\text{OH}} & & \text{H} & & \overset{(4)}{\text{OH}} & & \overset{(5)}{\text{OH}} & \\ & & | & & | & & | & & | & \\ \overset{(1)}{\text{CHO}} & — & \text{C} & — & \text{C} & — & \text{C} & — & \text{C} & —\overset{(6)}{\text{CH}_2\text{OH}} \\ & & | & & | & & | & & | & \\ & & \text{H} & & \underset{(3)}{\text{OH}} & & \text{H} & & \text{H} & \end{array} \qquad 1\,\frac{2\cdot4\cdot5}{3}\,6 \quad \text{or} \quad \frac{2\cdot4\cdot5}{3}$$

mannite is:—

$$\begin{array}{cccccccccc} & & \text{H} & & \text{H} & & \overset{(4)}{\text{OH}} & & \overset{(5)}{\text{OH}} & \\ & & | & & | & & | & & | & \\ \overset{(1)}{\text{CH}_2\text{OH}} & — & \text{C} & — & \text{C} & — & \text{C} & — & \text{C} & —\overset{(6)}{\text{CH}_2\text{OH}} \\ & & | & & | & & | & & | & \\ & & \underset{(2)}{\text{OH}} & & \underset{(3)}{\text{OH}} & & \text{H} & & \text{H} & \end{array} \qquad 1\,\frac{4\cdot5}{2\cdot3}\,6 \quad \text{or} \quad \frac{4\cdot5}{2\cdot3}$$

dulcite is:—

$$\begin{array}{cccccccccc} & & \overset{(2)}{\text{OH}} & & \text{H} & & \text{H} & & \overset{(5)}{\text{OH}} & \\ & & | & & | & & | & & | & \\ \overset{(1)}{\text{CH}_2\text{OH}} & — & \text{C} & — & \text{C} & — & \text{C} & — & \text{C} & —\overset{(6)}{\text{CH}_2\text{OH}} \\ & & | & & | & & | & & | & \\ & & \text{H} & & \underset{(3)}{\text{OH}} & & \underset{(4)}{\text{OH}} & & \text{H} & \end{array} \qquad 1\,\frac{2\cdot5}{3\cdot4}\,6 \quad \text{or} \quad \frac{2\cdot5}{3\cdot4}$$

In symmetrical molecules, this method furnishes a ready

[1] Maquenne, *Les sucres et principaux dérivés*, p. 14.

mode of distinguishing active from intramolecularly compensated compounds; for if the compound be completely symmetrical, then each symmetrically placed group must be at the same distance from one end of the chain as its fellow is from the opposite end. Therefore, if we call n the number of carbon atoms in the chain, in the case of the inactive compounds the sums of the figures above or below the line will be equal to, or a multiple of $(n + 1)$; with uneven numbers, where pseudo-asymmetry appears, the sums will be equal to, or a multiple of:—

$$\frac{n+1}{2}$$

For instance, in the case of *d*-saccharic acid, we have the formula:—

$$\frac{2 \cdot 4 \cdot 5}{3}$$

The sums of the figures in the upper and lower lines are 11 and 3. In this case, the number of carbon atoms in the compound n is six, so that $(n + 1)$ is seven. Neither 11 nor 3 is a multiple of 7, so the compound is active.

Mannite $\frac{4 \cdot 5}{2 \cdot 3}$; sums equal $\frac{9}{5}$; $(n+1)$ is 7; compound active.

Dulcite $\frac{2 \cdot 5}{3 \cdot 4}$; „ $\frac{7}{7}$; $(n+1)$ „ 7; „ inactive.

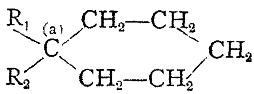
The formula of the optical isomer of mannite can at once be written down:—

Mannite is $1\,\frac{4 \cdot 5}{2 \cdot 3}\,6$; its isomer is therefore $1\,\frac{2 \cdot 3}{4 \cdot 5}\,6$

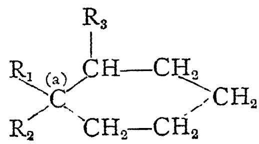
§ VIII. *THE ASYMMETRIC CARBON ATOM AS A MEMBER OF A RING.*

Just as an asymmetric carbon atom in an open chain compound produces optical activity, so the presence of one in a ring compound also tends to make it active. It appears at

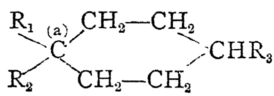
first somewhat strange that asymmetry can be produced in these circumstances, since apparently two valencies of the carbon atoms are united to one radical, and hence asymmetry seems absent. Two cases are possible in a ring compound: either the ring is symmetrical, or it is not. In the first case, no activity could be expected, since there is no asymmetric carbon atom; but if any substituent be introduced into the ring which makes it unsymmetrical, activity might arise. The figures below should make this clear:—



(1)



(2)



(3)

In the first case, if we consider the groups to which the carbon atom (a) is attached, we see that they are R_2; R_1; $CH_2—CH_2—CH_2—CH_2—CH_2—X$, counting clockwise; and $CH_2—CH_2—CH_2—CH_2—CH_2—X$, counting counter-clockwise round the ring (where X represents the rest of the molecule CR_1R_2). Here, the molecule contains no asymmetric carbon atom. The second case is different from the first, for here the groups are: R_1; R_2;

$$CH_2—CH_2—CH_2—CH_2—CHR_3—X$$

and $CHR_3—CH_2—CH_2—CH_2—CH_2—X$. Here the order in which the group R_3 appears in the chain is different in each case; so that the carbon atom (a) is really asymmetric, and the compound and its mirror image are not superposable upon one another. Case 3 shows that substitution need not always produce asymmetry, for on counting round the ring,

either clockwise or counter-clockwise, it will be found that the ring groups attached to the carbon atom are identical; and hence the carbon atom (a) is not asymmetric in this case.

§ IX. *CLASSIFICATION OF ISOMERS.*

Substances in which isomerism is due to the presence of an asymmetric carbon atom may be divided into three classes :—

1. Isomers with equal and opposite powers of rotation.

2. Isomers which, though optically active, have not equal and opposite actions upon polarized light.

3. Isomers which, though owing their isomerism to the presence of an asymmetric carbon, are not active.

The above classification, however, is not a convenient one for our present purpose, and in the following pages the inactive isomers containing an asymmetric carbon atom will be treated in one chapter, while another will be devoted to active isomers.

CHAPTER II.

INACTIVE COMPOUNDS.

A. Equimolecular Mixtures and Racemic Compounds.

§ I. *FORMATION.*

1. Production of Inactive Compounds containing an Asymmetric Carbon Atom. — When a compound of the type $Cabc_2$ is converted into another, $Cabcd$, which contains an asymmetric carbon atom, it might be supposed that an optically active substance would be formed. In practice, however, this is not the case: no activity can be detected in the product.

This can easily be explained. In the substance $Cabc_2$ we are dealing with an arrangement of atoms which may be expressed on the tetrahedral formula by Fig. 14, in which the two groups c are identical. Now, if one of these c's be replaced by d, we shall have a certain compound, and if the other c be chosen for replacement, we shall have the optical antipode of the first one (Fig. 15). But, as has already been mentioned, the two antipodes have identical chemical properties, and in physical properties differ only as regards crystalline form and action upon the plane of polarization. There is therefore no reason why one c should be replaced in preference to another; it is rather to be expected that the substitution will

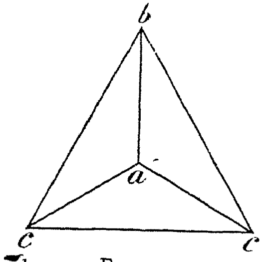


Fig. 14.

be distributed equally between the two. But if this be the case, then the reaction product will be a mixture of equal quantities of two substances which have equal and opposite actions upon

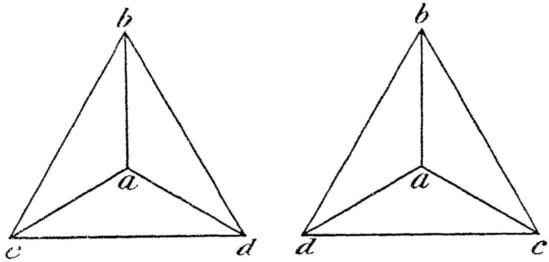
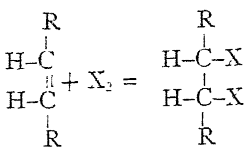


FIG. 15.

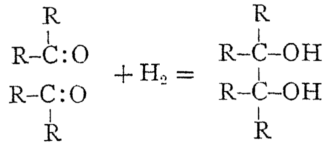
the plane of polarization; and hence no activity will be apparent.

It has been found that such an active body, made up of two molecules, of which one is dextro-, the other lævo-rotatory, may exist in three different forms. It may be simply a mechanical mixture of crystals of the two antipodes (*conglomerate*); it may be a crystalline body whose crystals are made up of alternate layers of the dextro- and lævo-substances (*mixed crystal*); or, finally, it may be a true chemical compound in which two molecules, one of the *d*-variety, the other of the *l*-isomer, have united with one another (*racemic compound*). In the case of the racemic compound, since true chemical combination has taken place, the molecular weight and other physical properties of the substance are different from those of mere mixtures of the antipodes.

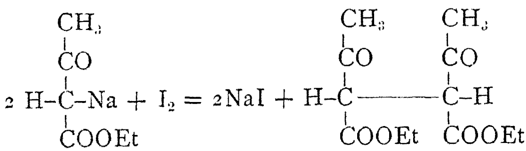
2. Production of Compounds with Two or more Asymmetric Carbon Atoms.—By many of the common methods of synthesising organic compounds, it is possible to produce substances which contain more than one asymmetric carbon atom. For instance, in the addition of halogens to unsaturated bodies, or in the production of pinacones; or, again, in the case of syntheses by means of acetoacetic ester, such substances are formed.



(1)



(2)



(3)

In these cases also inactive modifications are produced. Often the inactive substances are found in two forms, in one of which the inactivity is due to external compensation, as in the case described in the preceding paragraph, while in the second it is caused by internal compensation, due to the arrangement of the atoms within the molecule. This last type can only occur if the molecule be divisible into two symmetrical halves, as in the three cases shown above.

3. **Mixture of Antipodes.**—Enough has already been said to make it clear that an inactive solution may be formed by mixing equal quantities of two solutions containing optical antipodes; but at the same time it must be pointed out that the crystals formed from such solutions are not always chemical compounds of the antipodes, but are often merely physical mixtures. The influence of heat is very strongly marked in this case, as it is found that racemic compounds are produced only within a certain range of temperature. For example, in the case of potassium sodium tartrate it has been shown [1] that at temperatures below $-6°$, *d*- and *l*-tartrates exist in the solution together; above $-6°$, the potassium-sodium racemate begins to be formed; while about $41°$ it decomposes into potassium and sodium racemates.

[1] van't Hoff, Goldschmidt, and Jorissen, *Zeit. physikal. Chem.*, **17**, 505 (1895).

4. **Racemisation of Active Compounds.**—If an active substance be heated for a considerable time, its rotatory power decreases, and eventually, if the heating be continued long enough, the substance becomes inactive. No change in constitution, however, takes place during the process; but it would seem probable that the intramolecular stability of the substance is diminished by the raising of the temperature, and that thus a change in the configuration takes place which gives rise to the mirror image of the first compound. That the final product is actually an equimolecular mixture of the antipodes has been proved by Le Bel[1] and Lewkowitsch.[2] This process can be hastened by the presence of certain foreign substances—for example, tartaric acid is more easily racemised in presence of aluminium tartrate than when heated alone.[3]

Since the two antipodes have identical chemical properties, it is to be expected that their stabilities also would be the same, yet at first sight this does not appear to agree with the fact that when one isomer is converted into the other, equilibrium is reached only when both are present in equal quantity: the explanation probably is to be found in the fact that the conversion of the *d*-compound into the *l*-isomer proceeds with the same velocity as the inverse change of the *l*- into the *d*-form.

Racemisation may be brought about by simple heating, by heating with alkalies, by heating with acids, or in the course of some reactions. In certain cases it takes place spontaneously.

(*a*) *Explanation of Racemisation.*—If we assume that the valencies of a carbon atom are four distinct forces acting in certain directions, it is almost impossible to arrive at any satisfactory explanation of racemisation; for if the van 't Hoff hypothesis be used, it will be evident that a change of groups from one valency to another can only take place if these groups separate from the rest of the molecule and then unite

[1] Le Bel, *Bull. Soc. chim.*, [2] **31**, 104 (1879); *Compt. rend.*, **87**, 213 (1878).

[2] Lewkowitsch, *Ber.*, **15**, 1505 (1882).

[3] Jungfleisch, *Compt. rend.*, **85**, 805 (1877).

with it again in a different way. But this presupposes that certain secondary products are formed in the course of the reaction, no trace of which can be found in practice.

The explanation proposed by Werner[1] depends upon his own conception of the character of carbon valency. In Figure 16 the carbon atom is represented as a sphere, (I.), and the groups attached to it are supposed to be vibrating about the positions, *a*, *b*, *c*, and *d*. Now, under the influence of racemising agents, Werner assumes that these groups will not remain relatively fixed, but will move in vibrations of greater amplitude than before; and he assumes further that these vibrations will take place in the directions of the arrows in the diagram. In this way the groups will be brought into the position shown in the next figure, (II.), where they all lie in one plane. And now from this position they will either vibrate back into the original position, or take up the new one shown in the third diagram. If the latter movements take place, then a mirror image of the first figure is produced. Once the middle phase is reached, there is as much likelihood of one isomer being produced as of the other being formed.

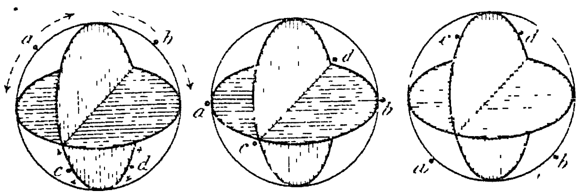


FIG. 16.

Nef[2] has put forward the theory that in certain compounds racemisation is brought about by loss of water from one carbon atom, which then adds on the water in another way, *e.g.*—

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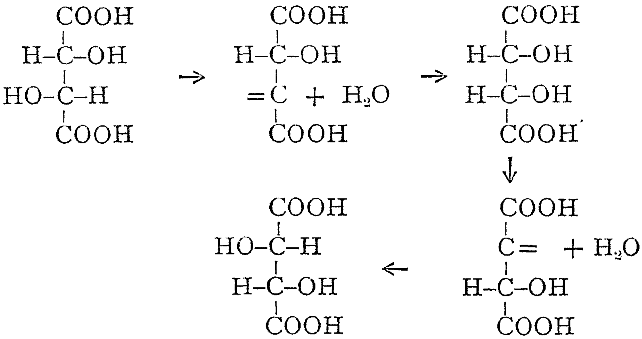
[1] Werner, *Beiträge zur Theorie der Affinität und Valenz.*
[2] Nef, *Annalen*, **335**, 191 (1904).



(*b*) *Autoracemisation.*—Walden[1] has described several cases, chiefly in the halogen-substituted fatty acids, where active compounds, after standing for three or four years, have been racemised; as far as can be ascertained, no change in constitution accompanies the alteration of the configuration. The change appears to be due to a permanent rearrangement of the radicals in the molecules, since the inactivity was not affected by fractionation or recrystallization.

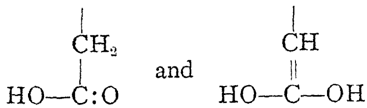
(*c*) *Racemisation as a Result of Changes in Constitution.*—It should be noted that replacement of one radical by another in a compound is often followed by racemisation. For example, *l*-mandelic acid, when treated with hydrobromic acid at a temperature not exceeding 50°, yields inactive phenylbromacetic acid. On the other hand, one compound can often be converted into another without losing its inactivity, if the conditions of the change do not lend themselves to racemisation. Pope and Harvey[2] have shown that *d*-ac-tetrahydro-*β*-naphthylamine is partially racemised during the process of formation of benzylidene-, benzoyl-, or acetyl-derivatives.

(*d*) *Relation between Tautomerism and Racemisation.*—Hitherto we have considered the phenomena of racemisation as not involving any change in the structure of the compounds concerned; but there is an alternative explanation of the

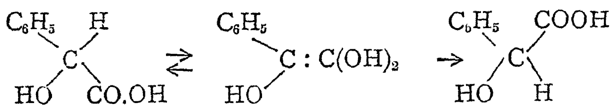
[1] Walden, *Ber.*, **31**, 1416 (1898).

[2] Pope and Harvey, *Proc.*, **16**, 74 (1900).

phenomena which may be given here. It is well known that the group —CH_2—CO— can be converted into —CH : C(OH)—, and *vice versâ* : and if this idea be applied to the case of racemisation, it explains some points which are not otherwise clear. If we consider the case of an acid which has a hydrogen atom in the α-position, the two tautomeric forms are :—

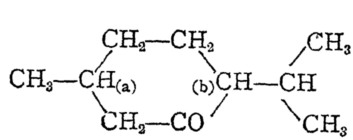


When we take the case of phenyl-glycollic acid, we find the following process possible—



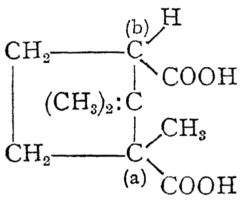
d-phenyl-glycollic acid (50 per cent.). inactive enolic form (trace). *l*-phenyl-glycollic acid (50 per cent.).

Here, through the intermediate enolic form, it is possible for the change from one active form into the other to take place. This explanation has strong evidence in its favour. It is clear that if the solution of the racemisation problem is to be sought in the phenomena of tautomerism, then only tautomeric substances will be capable of racemisation. If we consider the case of menthone :—

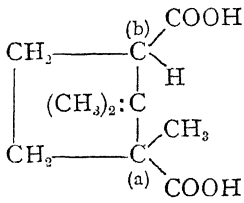


some insight into the matter may be obtained. Menthone contains two asymmetric carbon atoms (a) and (b), only one of which, (b), has a hydrogen atom attached to it which is capable of tautomerism. Now, when menthone is racemised, it is found that the change is due to one of the asymmetric atoms, viz. (b), the one adjacent to a carbonyl group. The other

asymmetric atom, (a), remains unattacked. A similar case is observed in the camphoric acids :—



Camphoric acid.



Isocamphoric acid.

Here, again, there are two asymmetric carbon atoms, (a) and (b), in the compound; and in this case also it is found that racemisation takes place only with (b), which has a free hydrogen atom in the α-position to the carboxyl group. That only one asymmetric carbon atom is altered can be shown in the following manner. Since *d*-camphoric acid is the mirror image of *l*-camphoric acid, it is evident that the conversion of the one into the other can take place only by the inversion of both asymmetric carbon atoms; whereas from the formulæ given above it appears that a change in the carbon atom (b) will suffice to convert camphoric acid into iso-camphoric acid. Now, in practice it is not possible to convert *d*-camphoric acid into *l*-camphoric acid; but only to change it into *d*-iso-camphoric acid; that is to say, it is only possible to change the configuration of the carbon atom (b). Similar conclusions may be drawn from the fact that in the acids of the sugar series, when racemisation occurs, it takes place always at the carbon atom next to the carboxyl group.

§ II. *CRITERIA OF THE NATURE OF EQUIMOLECULAR MIXTURES.*[1]

1. General.—An equimolecular mixture of optical antipodes can consist of (1) a *conglomerate*, or mixture of the two

[1] Cf. Findlay, *The Phase Rule and its Applications* in this series.

components with no chemical combination; (2) *mixed crystals*, found when the two compounds are isomorphous (here, also, there is no chemical combination); and (3) true *racemic compounds*, whose molecular weight is double that of the corresponding active isomer. It is necessary to be able to discover to which class a given compound belongs, and the matter is not easy. Many methods have been suggested; but, as Roozeboom[1] has shown, the melting-points and solubilities of the substances yield the most definite results. J. H. Adriani[2] has confirmed Roozeboom's views by a considerable amount of practical work. These properties, unfortunately, can be used only when the substance is solid, and in the case of liquid racemates no reliable method has been discovered. The following paragraphs will, therefore, deal only with solid racemates.

2. The Phenomena of the Melting-point.—(*a*) *Conglomerates.*—The melting-point of any solvent is lowered by the solution in it of a foreign substance. Now, if the relative amount of solvent be diminished, the same relation will still hold, until the melting-point reaches a minimum value. If the process be still maintained, the substance which was originally the solvent will now be the dissolved body, and thereafter the melting-point will rise instead of falling, since the proportion of the solvent to the solution is increasing. Applying this to the case of an equimolecular mixture of two optical antipodes which do not combine chemically with one another, we should find the following (see Fig. 17). If BA represents the melting-point of, say, the *d*-form, then as

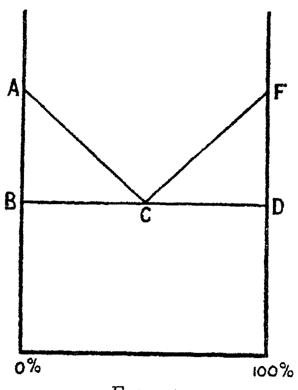


FIG. 17.

[1] Roozeboom, *Ber.*, **32**, 537 (1899); *Zeit. physikal. Chem.*, **28**, 494 (1899).

[2] Adriani, *Zeit. physikal. Chem.*, **33**, 453 (1900); **36**, 168 (1901).

some of the *l*-variety is gradually added the melting-point will fall until it reaches a minimum at C, when equal quantities of the *d*- and *l*-forms are present. Now let F represent the melting-point of the *l*-form; here also, as the other isomer is added, the melting-point will fall, until it also comes to that represented by the point C when the two antipodes are present in equal quantity. From the figure it is apparent that the melting-point is a minimum when the mixture is equimolecular, and that any addition of either isomer to this equimolecular mixture will produce a rise in the melting-point.

(*b*) *Mixed Crystals.*—A mixed crystal of two isomorphous optical antipodes exists only in a single phase, and the freezing-point of the liquid substance depends upon the composition of the crystals which first separate out. If their composition is the same as that of the fused substance, then mixtures of the two compounds in any proportions will have a constant melting-point. If, however, this be not the case, the melting-point will either rise or fall until it reaches that of an equimolecular mixture. It will rise if, in the crystals which first separate, the concentration of the second component is smaller than in the fused substance; and it will fall when the reverse is the case.[1]

(*c*) *Racemic Compounds.*—In the case of a racemic compound being formed, it is clear that since we are now dealing with three compounds we shall have two sets of curves, one showing the relations between the *d*-antipode and the racemic body, and the other illustrating those between the racemic compound and the *l*-isomer. The figures below show possible forms of the curves. This case is really a repetition of Case I. twice over; if the racemic compound be considered as taking the place of one or other of the antipodes, A represents the melting-point of the *d*-form, H that of the *l*-isomer, and D the racemate's. The abscissæ along BK represent graphically the percentages of *d*-isomer and racemic compound present, while those from K to G represent the percentages of racemate and

[1] Reasons for this need not be given here, as the matter is fully discussed in Findlay's *Phase Rule.*

l-antipode. It can at once be seen that an addition to the racemate of either *d*- or *l*-form will result in a lowering of the melting-point.

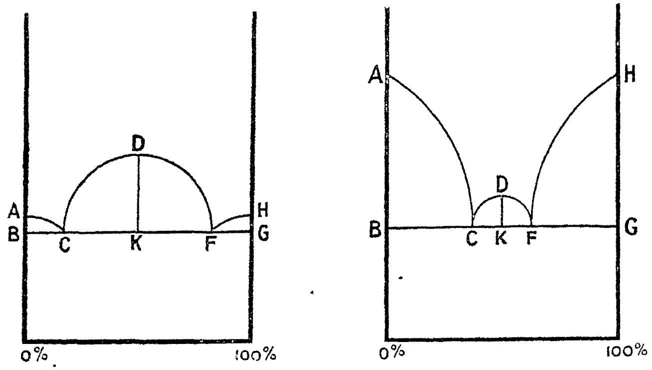


FIG. 18.

3. The Phenomena of Solution.[1]—When an inactive body is dissolved, it breaks up into the two antipodes, and therefore the solution forms a system of three components, the *d*-isomer, the *l*-isomer, and the solvent, and this system will only be in complete equilibrium at constant temperature when there are two solid phases. If the inactive body be a conglomerate, it already exists in two phases, and the addition of either active isomer to the solution will produce no change in the solubility. On the other hand, if the inactive substance be a chemical compound or a solid solution, there will be only one solid phase, and the addition of one antipode will alter the solubility.

Bruni [2] suggested another method for determining whether a compound, conglomerate, or mixed crystal be present. He points out that when the cryohydric curves of the three cases are drawn, that of the racemic compound will have three branches, the curve of the conglomerate having two and that of the mixed crystal only one. Bruni and Finzi [3] carried out

[1] Roozeboom, *Zeit. physikal. Chem.*, **28**, 496 (1899).
[2] Bruni, *Gazzetta*, **30**, i. 35 (1900).
[3] Bruni and Finzi, *Atti R. Accad. Lincei*, [5] **13**, ii. 349 (1904).

a series of researches in the following manner. To the cryohydric solution of the inactive substance, portions of the *d*- or *l*-variety are added in gradually increasing quantity. If the inactive body is a conglomerate, the freezing-point remains constant. If a true racemic compound be present, the freezing-point sinks through a certain interval and then remains constant even when further quantities of the active substance are added. The solution is then evaporated to dryness and weighed; after this the quantities of inactive and active substances present may be calculated from its rotatory power; and from these data the curves of equilibrium may be drawn. If the inactive substance be a pseudo-racemic mixed crystal, the freezing-point and the rotatory power will change with each addition of active substance to the solution.

§ III. *THE PROPERTIES OF RACEMIC COMPOUNDS.*

1. **Physical.**—*Molecular Weight.*—When cryoscopic methods are employed to find the molecular weight of a racemate, the depression of the freezing-point is found to be the same as if one antipode had been used;[1] from which it appears that in solution the racemic substance breaks down into the two antipodes. G. Bruni and M. Padoa[2] state that they have obtained evidence in favour of the existence of racemic compounds in solution. The vapour density method yields negative results. From the fact that racemic compounds are optically inactive, however, it must be concluded that they are produced by the union of two active molecules of opposite rotations; and it therefore follows that the solid racemic compound has a molecular weight double that of one active component.

Crystalline Form.—In the majority of cases this differs from that of the optical antipodes; generally the racemic compounds crystallize in holohedral forms, while the active

[1] Raoult, *Zeit. physikal. Chem.*, **1**, 186 (1887); Anschutz, *Annalen*, **247**, 121 (1888); Wallach, *ibid.*, **246**, 231 (1888).

[2] Bruni and Padoa, *Atti R. Accad. Lincei*, [5] **11**, i. 212 (1902); *Gazzetta*, **32**, i. 503 (1902).

substances appear in hemihedral crystals. The active isomers and the corresponding racemic compound do not always belong to the same crystalline system; *e.g.* the active carvone tetrabromide occurs in rhombic crystals, while the crystalline form of the racemic compound is monoclinic.

Specific Gravity.—Liebisch[1] and Walden,[2] as well as Wallach,[3] have examined this point, and find that in general the inactive substances have a greater density than the active ones.

Molecular Volume.—The form with the lower melting-point appears to have the greater molecular volume of the two.[4]

Solubility and Melting-point.—These show a certain relation to the respective densities of the active and racemic substances: the substance which has the greater density having also the higher melting-point and lesser solubility.[4]

Absorption Spectra.—These have been found by Stewart to be different for the active and racemic forms.

Triboluminescence.—It appears from the researches of Tschugaeff[5] that some active compounds, when rubbed or struck, give phosphorescence, while in the case of the corresponding racemic substances no such effect is observed.

*Affinity Constants.**—According to Walden[4] these are the same for both active and racemic forms. This is probably due to the dissociation of the racemic acid into the two antipodes from which it was formed.

2. Chemical.—*Water of Crystallization.*—Usually there is a considerable difference in the amounts of water of crystallization in the cases of active and racemic compounds, but there appears to be no general rule.

Chemical Behaviour.—Generally the two sets of compounds have the same chemical properties, but in one or two instances

* If we represent the degree of dissociation of an acid by m, and the dilution of its solution by v, then its affinity constant $k = \frac{m^2}{(1 - m)v}$.

[1] Liebisch, *Annalen*, **286**, 140 (1895).

[2] Walden, *Ber.*, **29**, 1699 (1896).

[3] Wallach, *Annalen*, **286**, 135 (1895).

[4] Walden, *Ber.*, **29**, 1692 (1896).

[5] Tschugaeff, *Ber.*, **34**, 1820 (1901).

deviations have been observed. For instance, Anschütz and Bennert[1] noticed that the ethyl ester of *l*-malic acid breaks down when distilled at ordinary pressure, while the inactive ester distils over unchanged under the same conditions.

§ IV. *LIQUID RACEMIC COMPOUNDS.*

When equal quantities of two optical antipodes are mixed together, either of two results may follow: for the mixture may remain a mere mechanical mixture, or the two substances may combine with one another and form a true racemic compound. In some particular instances we are able to discover what has taken place, owing to the physical properties of the racemic compound being markedly different from those of the antipodes from which it is formed. For instance, the dextro- and lævo-forms of carone oxime melt at 72° C., while racemic carone oxime has a melting-point of 93° C.; so that if we heat the active forms to any temperature between 72° C. and 93° C., and then mix them, the solid racemic compound will crystallize out.[2] But if, on the other hand, the physical constants of the mixture of antipodes remain identical with those of the original active compounds, it becomes a matter of extreme difficulty to prove the actual existence of a racemic compound. Attempts have been made to draw deductions from the changes of temperature brought about at the moment of mixing, but nothing certain has been found; while cryoscopic methods and investigations of the boiling-points of the inactive mixtures have not added anything of importance to our knowledge. Stewart has found that while the absorption spectra of dextro- and lævo-tartaric acid are identical, a much greater absorptive power is shown by a mixture of their solutions in equal strength. Since this change in spectrum can only indicate a change in constitution, this method appears likely to be of some value in the examination of inactive substances.

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[1] Anschutz and Bennert, *Annalen*, **254**, 164 (1889).

[2] Baeyer, *Ber.*, **28**, 640 (1895).

§ V. *LIMITS OF THE EXISTENCE OF RACEMIC COMPOUNDS.*

As has been pointed out already, if a crystalline substance is inactive, it may be (1) a conglomerate, (2) a mixed crystal, or (3) a true chemical compound. Now, it is possible that when the temperature is raised, these states may not be stable; and in practice it is found that a racemic compound may be thus converted into a conglomerate or a solid solution; or the reverse change of conglomerate or solid solution into a racemic compound may occur. The first observation in the subject was made by Pasteur, who found that by crystallizing sodium ammonium racemate he was able to separate the *d*- and *l*-tartrates from one another. Staedel,[1] repeating Pasteur's work, was unable to do this, and found that the crystals which he obtained were merely those of the racemate. Scacchi[2] explained this apparent contradiction by showing that crystallization above a certain temperature produced crystals of the racemic compound, while below this temperature the crystals of the two tartrates separate out. Wyrouboff[3] showed that this temperature was 28° C. Such a temperature is termed the *Transition Temperature* of the substance in question. It was found by van't Hoff and Deventer[4] that this process was not confined to substances in solution, but held good in the case of crystals heated in sealed tubes.

B. COMPOUNDS WHICH ARE INACTIVE THROUGH INTERNAL COMPENSATION.

§ I. *THEORETICAL.*

It has been pointed out already that inactivity does not necessarily imply the absence of asymmetric carbon atoms

[1] Staedel, *Ber.*, **11**, 1752 (1878).

[2] Scacchi, *Rend. Accad. Sci. Fis. Mat. Napoli*, **1865**, 250.

[3] Wyrouboff, *Bull. Soc. chim.*, [2] **41**, 210 (1884); **45**, 52 (1886); *Compt. rend.*, **102**, 627 (1886).

[4] van't Hoff and Deventer, *Zeit. physikal. Chem.*, **1**, 165 (1887).

from a compound; for it may be produced either by a mixture of two groups of molecules whose powers of rotation are equal and opposite, or by the fact that the two halves of a molecule have equal and opposite effects on polarized light. The latter class of compound is called the *internally compensated* variety, in contradistinction to the *externally compensated* or racemic type.

In order that any compound may be internally compensated, it is necessary that its molecule should be divisible into two halves, which are related to one another in configuration as an object to its mirror image. Now, if this be the case, it follows that the molecules in question will possess a plane of symmetry, and hence will not appear in enantiomorphous forms. For instance, in the case of mesotartaric acid, though at first sight it seems as if the configuration (I.) and its mirror image (II.) were different, it is only necessary to imagine the second figure turned through an angle of 180° in order to make the two coincide, which could not be done if there was enantiomorphism.

$$\begin{array}{ccc} \begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{COOH} \\ \text{(I.)} \end{array} & \qquad & \begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{COOH} \\ \text{(II.)} \end{array} \end{array}$$

Compounds of this type cannot be made active by any of the methods which succeed in the case of externally compensated substances; it is only by destroying the symmetry of the molecule itself that the result can be attained: *e.g.* when mucic acid is reduced to galactonic acid:

$$COOH.CH(OH).CH(OH).CH(OH).CH(OH).COOH \longrightarrow CH_2OH.CH(OH).CH(OH).CH(OH).CH(OH).COOH$$

The fact that mesotartaric acid has a lower melting-point than racemic acid, is sometimes utilised to distinguish one

isomer from another: those like mesotartaric acid being called *Anti-forms* and the others *Para-forms*. This is not a particularly happy nomenclature, since in many cases the intramolecularly compensated type has a higher melting-point than the externally compensated substance.

§ II. *THE PREPARATION OF INTERNALLY COMPENSATED COMPOUNDS.*

There are no general methods for the preparation of this class of substances; and as comparatively few of the type have been studied, only some isolated facts can be given here. Mesotartaric is obtained by heating *d*-tartaric acid with cinchonine to 170° C.[1]; by long-continued heating of *d*-tartaric or racemic acid to 170° C. or 180° C.; by boiling active tartaric or racemic acid with hydrochloric or sulphuric acid for four hundred hours[2]; and by heating the active or racemic acid for two days in a sealed tube with water (four grammes water to thirty grammes acid) to a temperature of 165° C., which must not be exceeded.[3] Meso-tartaric acid is also obtained by the oxidation with nitric acid of inactive erythrite, which in its turn is produced by the reduction of dextro-erythrose. Holleman[4] has made a detailed study of the changes which the active, meso-, and racemic forms of tartaric acid can be made to undergo. His principal results are as follows. The action of hydrochloric acid upon the three compounds was studied, using temperatures ranging from 109° C. to 155° C. and various reaction times. Below 155° C., the dextro-acid yields more meso-tartaric than racemic acid. The meso- and racemic forms are capable of transformation into one another, but neither will yield the dextro-form by this method. When a hundred grammes of dextro-tartaric acid are boiled for three

[1] Pasteur, *Compt. rend.*, **37**, 162 (1853).

[2] Dessaignes, *ibid.*, **55**, 769 (1862); *Bull. Soc. chim.*, **3**, 34 (1862); **5**, 356 (1863).

[3] Jungfleisch, *Bull. Soc. chim.*, **19**, 101 (1873).

[4] Holleman, *Rec. trav. chim.*, **17**, 66 (1898).

hours under a reflux condenser with three hundred and fifty grammes of sodium hydrate dissolved in seven hundred grammes of water, fifty grammes of racemic acid and thirty of meso-tartaric are produced, twenty grammes of the active acid remaining unchanged.

§ III. *THE PROPERTIES OF INTERNALLY COMPENSATED COMPOUNDS.*

Internally compensated compounds differ to a considerable extent from the corresponding externally compensated forms. The specific gravities, solubilities, melting-points, and affinity constants appear to be different in each case. The following table gives examples :—

	Racemic acid.	Mesotartaric acid.
Melting-point[1]	206·0°	140·0°
Affinity constant[2]	0·097	0·060
Density	1·697	1·666
Solubility in 100 parts of water at 15°[3] .	17·1	125·0
Water of crystallization of the calcium salt[4] .	4 molecules	3 molecules

Differences in other properties are found in the case of the tri-hydroxy-glutaric acids. The internally compensated variety (1) can easily be isolated in the form of a lactonic acid; the active (2) and the second intramolecularly compensated type (3) do not yield lactones in this way :—

(I.)	(II.)	(III.)
COOH	COOH	COOH
H.OH	H.OH	H.OH
H.OH	H.OH	HO.H
H.OH	HO.H	H.OH
COOH	COOH	COOH

[1] Bischoff and Walden, *Ber.*, **22**, 1815 (1889).

[2] Walden, *Ber.*, **22**, 1820 (1889); Ostwald, *Zeit. physikal. Chem.*, **3**, 372 (1889).

[3] Bischoff und Walden, *Ber.*, **22**, 181 (1889).

[4] Anschutz, *Annalen*, **226**, 197 (1884).

CHAPTER III.

ACTIVE COMPOUNDS.

A. Optical Antipodes.

§ 1. *PROPERTIES OF OPTICAL ANTIPODES.*

It is still uncertain whether or not an optically active compound has a crystalline form distinct from that of its antipode. Walden [1] and Wyrouboff [2] have answered the question in the negative, while Traube [3] and Becke [4] take the opposite view. Until much more material has been accumulated than is at present at our disposal, the matter cannot be examined with any hope of success.

Two optical antipodes have the same specific gravity, molecular volume, boiling-point, melting-point, solubility, heat of solution, of combustion, and of neutralization. They have the same affinity constant and index of refraction; their absorption spectra also appear to be the same.[5]

The most important difference between two antipodes has been demonstrated by Cotton,[6] who has shown that *d*-circularly polarized light is differently absorbed by the *d*- and *l*- varieties of copper ammonium tartrate. Byk [7] points out that light is circularly polarized by the surface of the sea, and that one

[1] Walden, *Ber.*, **29**, 1692 (1896).

[2] Wyrouboff, *Ann. Chim. Phys.*, [6] **8**, 416 (1885); [7] **1**, 10 (1894).

[3] Traube, *Ber.*, **29**, 2446 (1896).

[4] Becke, *Tsch. Min. Mitth.*, **10**, 414 (1891); **12**, 256 (1892).

[5] Hartley and Huntington, *Proc. Roy. Soc.*, **1881**, 1; Magini, *J. Chim. physique*, **2**, 403 (1904).

[6] Cotton, *Ann. Chim. Phys.*, [7] **8**, 373 (1896).

[7] Byk, *Zeit. physikal. Chem.*, **49**, 641 (1904); *Ber.*, **37**, 4696 (1904).

variety of this light predominates on the earth's surface. This preponderance of *d*-light may possibly be more favourable to the persistence of one variety of an active acid; if this were so, an explanation of the production of active bodies in nature would be found.

A curious thermo-electric effect is observed when crystals of dextro- and lævo-tartaric acid are cooled after being warmed. In the case of the one isomer, pyro-electricity is generated on the right hand of the crystal, while in the other isomer it makes its appearance on the left-hand side.

As a rule, both optical antipodes have exactly the same chemical actions upon inactive bodies. A few statements to the contrary are to be found in the literature, but it is possible that they may be due to errors of observation.

On the other hand, when an *active* substance reacts with one of two optical isomers the velocity of the reaction is not the same in the case of each isomer. In this case a new asymmetric complex has been introduced into the molecule, and it produces marked differences in behaviour in the two new compounds. For example, suppose that a mixture of a *d*- with an *l*-acid has been added to a *d*-base, and let the rotation of the acid be A, while that of the base is B. Then, in the two cases we shall have two new substances of different rotations, one being (B + A) and the other (B − A). It is evident that the two new compounds are not antipodes, and that hence probably their solubilities and other physical properties will be different from one another.

§ II. *FORMATION.*

1. From Equimolecular Mixtures.—The methods which can be classed under this heading were discovered by Pasteur; they are three in number, depending on (*a*) spontaneous separation of the antipodes, (*b*) biochemical methods, and (*c*) salt formation with active acids or bases. Several modifications of these methods have been devised by various workers; these methods also will be described.

(*a*) *Spontaneous Separation.*—It has already been pointed out that inactive mixtures of the two antipodes are not always chemical compounds, but are often merely mechanical mixtures. If in such a case the antipodes do not form mixed crystals, it will be possible to separate one from the other by a process of simple crystallization. From what has already been said, it will be apparent that attention must be paid to the transition temperature of the substance in question. This method has not a wide application, as it is not so convenient as the other methods which are available.

(*b*) *Biochemical Methods.*—It was first observed by Pasteur[1] that when the ferment *Penicillium glaucum* was allowed to grow in a solution of ammonium racemate, it destroyed the *d*-isomer and left the *l*-ammonium salt. Many similar experiments showed that this method of separation was capable of a wide application; but since Pasteur's work the only advance in the biochemical method has been made by the discovery of new fungi which have the property of separating one isomer from another. Since concentrated solutions of the undecomposed antipode have an injurious effect on the ferments used, it is necessary to work with dilute solutions, to which ammonium salts and phosphates must be added to furnish nourishment for the organism. The biochemical methods have the disadvantage that at best only half the racemic compound can be obtained in the active condition, and in most cases the yield is much less than this; while the isolation of the active compound from dilute solution adds another difficulty to the work. The method has most application as a qualitative test to determine whether or not a substance can be made active at all; but as a method of preparation it is only utilised when every other has failed. It was at one time supposed that the action of fungi was confined entirely to one isomer, the other being left unattacked. It has since been shown by McKenzie and Harden[2] that this is not the case; but that, instead, both isomers are attacked, though at very different rates.

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[1] Pasteur, *Compt. rend.*, **32**, 110 (1851); **36**, 26 (1853); **37**, 110, 162 (1853).

[2] McKenzie and Harden, *Trans.*, **83**, 424 (1903).

(*c*) *Salt Formation with Active Bases or Acids.*—This method was also discovered by Pasteur. When a solution of racemic acid is saturated with cinchonine and slowly evaporated, it is found that the first crystals which separate out are composed of the cinchonine salt of *l*-tartaric acid, while cinchonine *d*-tartrate remains in solution. The reason for this will be apparent when the results of salt formation are considered. If the acid be denoted by A and the base by B, while the left and right rotatory powers are indicated by + and −, we have:—

$$\begin{array}{ccccc} (A+) & + & (B+) & = & (A+B+) \\ (A-) & + & (B+) & = & (A-B+) \end{array}$$

These two resulting compounds are not mirror-images, and it is therefore unlikely that their solubilities will be identical, like those of the two original acids. The one salt will therefore crystallize out before the other. The crystallization sometimes requires to be aided by the addition of a crystal of the less soluble form. Marckwald[1] has improved this method by utilizing both active forms of a base or acid; he proceeds as above in the first instance, and after separating out as much of the one salt as possible, he converts the residue into the salt of the opposite isomer, and by crystallization is thus able to obtain the second constituent of the racemic compound in a state of purity. The utility of various active acids and bases appears to be proportional to their rotatory power. The natural bases may be divided into two classes, the members of one yielding sparingly soluble salts of one isomer, while the second antipode can be obtained by using those in the other class. For example:—

Class I.—Quinine, strychnine, and brucine.

Class II.—Cinchonine, cinchonidine, and morphine.

(*d*) *Relations between the Results of Biochemical Resolution and those obtained with Active Acids and Bases.*—Winther[2] has pointed out that there is a striking analogy between the effect of certain ferments and that of some alkaloids; and from the

[1] Marckwald, *Ber.*, **29**, 43 (1896).

[2] Winther, *Ber.*, **28**, 3016 (1895).

examples given by him it appears that if a ferment and a base applied to one racemic substance yield the same antipode, when the same two agents are used upon another racemic compound they will in that case also give rise to the same isomer. The table below shows a few instances from the organic acids. Column I. shows the isomer which is destroyed by the ferment *Penicillium glaucum*; column II. contains the isomers which form the more sparingly soluble salts with strychnine; the third column gives those compounds destroyed by Lewkowitsch's *Schizomycete*; while in the last column are placed the antipodes which give sparingly soluble salts with cinchonine.

I.	II.	III.	IV.
d-tartaric	—	*l*-tartaric	*l*-tartaric
l-ethoxysuccinic	*l*-methoxysuccinic	—	*d*-methoxysuccinic
l-mandelic	—	*d*-mandelic	*d*-mandelic
l-lactic	*l*-lactic	—	—

It cannot as yet be decided what meaning should be attached to this resemblance, and it seems desirable that some work should be done on the point, in order to clear up the question.

(*e*) *Formation of Esters, or their Hydrolysis.*—It has been mentioned already that when two optically active isomers react with an inactive body, no differences need be looked for between the two reactions; but if for the inactive substance we substitute an active one, the conditions are altered, and there will be a divergence not only between the properties of the final products, but also between the ways in which the two reactions proceed. It will be shown in a later part of this book that the space relations of atoms appear to exert a great influence upon the velocities of some reactions; here we need mention only Menschutkin's results in the case of the esterification of fatty acids.[1] He found that the velocity of

[1] Menschutkin, *Jour. Russ. Phys. Chem. Soc.*, **13**, 573 (1881).

esterification of acids of the type $R.CH_2.COOH$ was approximately twice as great as that of acids like :—

$$\begin{matrix} R \\ R_1 \end{matrix} CH.COOH$$

and much greater than that of acids of the class :—

$$\begin{matrix} R \\ R_1—C.COOH \\ R_2 \end{matrix}$$

From this it appeared possible that a somewhat similar result might be expected in the case of those compounds whose atoms were differently arranged in space. Marckwald and McKenzie[1] tested this with racemic mandelic acid and menthol, interrupting the process before it was complete, and found that *l*-menthol actually does combine more slowly with *l*-mandelic acid than with *d*-mandelic. The possibility of applying this process of separation has thus been demonstrated; and the authors mentioned have utilised the inverse method of hydrolysis in a somewhat similar manner, esters of the types *d*-acid-*d*-alcohol and *d*-acid-*l*-alcohol being hydrolysed with different velocities, and thus forming an active product from an equimolecular mixture of the two.

(*f*) *Combination of Active Aldehydes with Racemic Bases.*—E. Erlenmeyer, jun., and A. Arnold[2] employed an active aldehyde to resolve a racemic base, in the following manner. They used the active aldehyde helicin, which is salicylaldehyde-glucose: $C_6H_{11}O_5\,O.C_6H_4CHO$; and as a racemic base they chose iso-diphenyl-hydroxyethylamine :—

$$C_6H_5.CH(OH).CH(NH_2).C_6H_5$$

The compound of the two :—

$$\begin{array}{l} C_6H_5—CH.OH \\ \qquad\quad\ | \\ C_6H_5—CH.N:CH.C_6H_4.O.C_6H_{11}O_5 \end{array}$$

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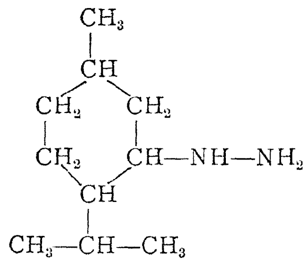
[1] Marckwald and McKenzie, *Ber.*, **32**, 2130 (1899).

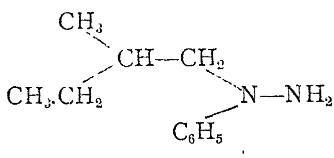
[2] Erlenmeyer, jun., *Ber.*, **36**, 976 (1903); Erlenmeyer, jun., and Arnold, *Annalen*, **337**, 307 (1904).

separated into two parts when the alcoholic solution of the compound was evaporated *in vacuo.* The crystalline portion contained the part derived from the dextro-base: while the amorphous portion proved to be a derivative of the lævo-base. The two active isomers were obtained by treating the two condensation products with very dilute hydrochloric acid, which split off the active radical.

(*g*) *Combination of Active Hydrazines with Racemic Aldehydes or Ketones.*—Neuberg[1] utilised active hydrazines for the same purpose, using lævo-menthyl-hydrazine:—



to resolve the racemic aldehyde arabinose. In this case also the intermediate compound (here a hydrazone) was separated into two portions, one of which yielded the dextro-, the other the lævo-aldehyde. Neuberg and Federer[2] have successfully employed *d*-amylphenylhydrazine for the same purpose:—



(*h*) *Amide Formation from Acids and Bases.*—Marckwald and Meth[3] showed that when a racemic acid was partially converted into an amide by heating it with an active amine, the

[1] Neuberg, *Ber.*, **36**, 1192 (1903).
[2] Neuberg and Federer, *Ber.*, **38**, 866, 868 (1905).
[3] Marckwald and Meth, *Ber.*, **38**, 801 (1905).

uncombined acid was active. For instance, they heated racemic mandelic acid with lævo-menthylamine for ten hours to 160–170° C., and found that 36 per cent. of the acid was converted into the amide. The remaining 64 per cent. of acid was found to have a specific rotation of $[\alpha]_D = -5{\cdot}1°$. Marckwald and Meth found that the relative speed of amide formation of lævo-menthylamine with dextro- and lævo-mandelic acid is expressed by $c = 0{\cdot}862$.

2. Biochemical Production of Active Bodies from Inactive Ones.—Bertrand[1] has devised a biochemical method which is of some interest, though at present its application appears to be limited to the production of active ketoses from inactive poly-alcohols. He employs as an agent the sorbose bacterium, which has oxidising properties; and he has studied its action upon glycol, xylite, dulcite, glycerol, *l*-erythrite, *l*-arabite, *d*-sorbite, *d*-mannite, perseite, and volemite. The first three of these bodies are not attacked by the ferment; the others are oxidised, those which contain a multiple of three carbon atoms being most easily broken down. The oxidation takes place at a secondary alcoholic group next to the primary one; and only those poly-alcohols are attacked which in their stereo-formula have no hydrogen atom adjacent to the oxidised hydroxyl radical: *i.e.* the oxidisable alcohols contain the group :—

$$\begin{array}{ccccc} & \mathrm{H} & & \mathrm{H} & \\ & | & & | & \\ — & \mathrm{C} & — & \mathrm{C} & —\mathrm{CH_2OH} \\ & | & & | & \\ & \mathrm{OH} & & \mathrm{OH} & \end{array}$$

while the unoxidised ones have, instead, the group :—

$$\begin{array}{ccccc} & \mathrm{OH} & & \mathrm{H} & \\ & | & & | & \\ — & \mathrm{C} & — & \mathrm{C} & —\mathrm{CH_2OH} \\ & | & & | & \\ & \mathrm{H} & & \mathrm{OH} & \end{array}$$

Since glycol, $CH_2OH.CH_2OH$, contains no secondary alcoholic

[1] Bertrand, *Bull. Soc. chim.*, [3] **19**, 347, 947, 999 (1898).

group, it is not attacked; in xylite and dulcite the hydrogen atoms marked with an asterisk, lying as they do in the position adjacent to the hydroxyl which should be attacked, act as a protection in some way not yet clearly understood.

Xylite :—

$$
\begin{array}{ccccccccc}
 & & & \mathrm{H} & & \mathrm{OH} & & \mathrm{H} & \\
 & & & | & & | & & | & \\
 & & \mathrm{CH_2OH}- & \mathrm{C} & - & \mathrm{C} & - & \mathrm{C} & -\mathrm{CH_2OH} \\
 & & & | & & | & & | & \\
\text{Point of attack} & \rightarrow & & \mathrm{OH} & & \mathrm{H} & & \mathrm{OH} & \leftarrow \text{Point of attack} \\
 & & & & & (*) & & &
\end{array}
$$

Dulcite :—

$$
\begin{array}{ccccccccccc}
 & & & \mathrm{H} & & \mathrm{OH} & & \mathrm{OH} & & \mathrm{H} & \\
 & & & | & & | & & | & & | & \\
 & & \mathrm{CH_2OH}- & \mathrm{C} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{C} & -\mathrm{CH_2OH} \\
 & & & | & & | & & | & & | & \\
\text{Point of attack} & \rightarrow & & \mathrm{OH} & & \mathrm{H} & & \mathrm{H} & & \mathrm{OH} & \leftarrow \text{Point of attack} \\
 & & & & & (*) & & (*) & & &
\end{array}
$$

On the other hand, if we write out the formulæ of those compounds which are attacked by the sorbose bacterium, we find that this sheltering hydrogen is absent from them all. The hydroxyl group attacked by the ferment is marked with a dagger in each case.

Glycerol :—

$$
\begin{array}{ccc}
 & (\dagger)\mathrm{OH} & \\
 & | & \\
\mathrm{CH_2OH}- & \mathrm{C} & -\mathrm{CH_2OH} \\
 & | & \\
 & \mathrm{H} &
\end{array}
$$

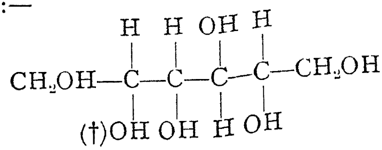
Erythrite :—

$$
\begin{array}{ccccc}
 & \mathrm{H} & & \mathrm{H} & \\
 & | & & | & \\
\mathrm{CH_2OH}- & \mathrm{C} & - & \mathrm{C} & -\mathrm{CH_2OH} \\
 & | & & | & \\
 & (\dagger)\mathrm{OH} & & \mathrm{OH}(\dagger) &
\end{array}
$$

l-Arabite :—

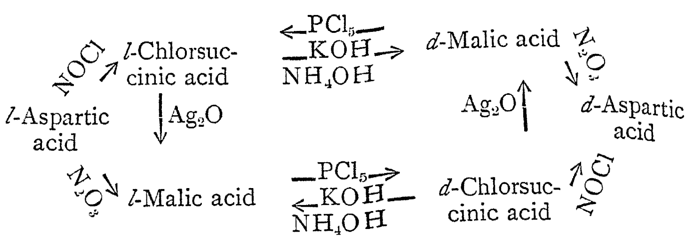
$$
\begin{array}{ccccccc}
 & (\dagger)\mathrm{OH} & & \mathrm{OH} & & \mathrm{H} & \\
 & | & & | & & | & \\
\mathrm{CH_2OH}- & \mathrm{C} & - & \mathrm{C} & - & \mathrm{C} & -\mathrm{CH_2OH} \\
 & | & & | & & | & \\
 & \mathrm{H} & & \mathrm{H} & & \mathrm{OH} &
\end{array}
$$

d-Sorbite :—



3. Production of one Optical Antipode from Another.—There are two ways in which one optical isomer may be obtained from its antipode. In the first, the optically active body is racemised by any of the methods already mentioned, and then the second isomer is separated from the racemic substance. This mode of solving the problem requires no further explanation.

There is, however, a second way in which the same object may be attained. Walden[1] has found that when, in an active compound, one radical is replaced by another, the configuration of the new compound may be influenced by the nature of the reagent used to bring about the replacement. For example, when *l*-chlorosuccinic acid is treated with dilute potash it yields *d*-malic acid; while if silver hydroxide be used instead of potash, *l*-malic acid is formed. Silver hydroxide and caustic potash are therefore different in their stereo-chemical effects. Walden has found that the basic hydroxides differ very much in their effects upon halogen-substituted fatty acids. A general scheme of the transformations of various acids will give some idea of the complexity of the problem.



It will be at once evident that it is possible to pass through a

[1] Walden, *Ber.*, **26**, 213 (1893); **28**, 1287, 2771 (1895); Walden and Lutz, **30**, 2795; Walden, **30**, 3146 (1897); **32**, 1833, 1855 (1899).

cycle of changes from one isomer to the other, the process being termed *optical inversion*.

Armstrong[1] has attempted to explain the mechanism of this process. When the inversion is brought about by hydrolytic agents, a keto-group in the compound (supposed to be an aldose, ketose, or acid) first becomes hydrated, forming an "aldehydrol,"—$CH(OH)_2$, or a "ketohydrol,"—$C(OH)_2$—, or an "acid-hydrol,"—$C(OH)_3$. When water is withdrawn from such compounds, if the water be formed from an OH-group of the hydrol complex and a hydrogen atom attached to the carbon contiguous to that of the hydrol complex, an ethenoid derivative will be formed; thus :—

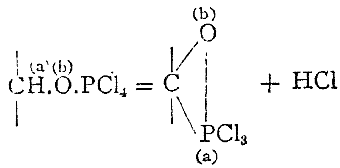
$$\begin{array}{l}\text{—CH.OH}\\ \quad|\\ \text{CO.OH}\end{array} + H_2O = \begin{array}{l}\text{—CH.OH}\\ \quad|\\ C(OH)_3\end{array} = \begin{array}{l}\text{—C.OH}\\ \quad\|\\ C(OH)_2\end{array} + H_2O$$

(In the present state of our knowledge it seems unnecessary to assume this step since a mere tautomeric change would suffice to bring about the same result.) On hydration, according as hydration takes place at one or the other junction of the ethenoid linkage, such a compound will afford one or other of the two possible asymmetric forms; and if, as in the case of tartaric acid, the compound be symmetrical, it is to be expected that the two forms will be produced in equal proportions. But if an unsymmetrical compound be thus changed, such as a hexose or an acid like gluconic acid, it is to be expected that the severance will take place to a greater extent at one of the two junctions, and in some cases perhaps only at one. When malic acid is acted on by phosphorus pentachloride, probably the first action to occur is one involving the formation of a chlorophosphonium compound; thus :—

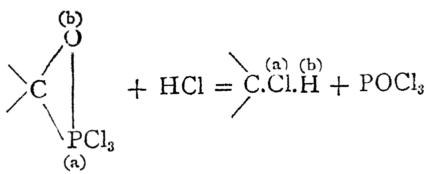
$$\begin{array}{l}|\\ \text{CH.}\overset{(a)}{\text{O}}\overset{(b)}{\text{H}}\\ |\end{array} + PCl_5 = \begin{array}{l}|\\ \text{CH.}\overset{(a)}{\text{O}}\overset{(b)}{.}PCl_4\\ |\end{array} + HCl$$

The next stage in the change may be assumed to be one involving internal condensation :—

[1] Armstrong, *Proc.*, **12**, 45 (1896).



Supposing that this compound be then acted on by hydrogen chloride and resolved into chlorosuccinic acid and phosphorus oxychloride, if the attack became *directed* by the phosphorus, so that the chlorine took up the position of the phosphorus, complete inversion would be effected :—



4. **Asymmetric Synthesis.**—In an *asymmetric synthesis* an active compound serves as a starting-point, to which a new radical is added in such a way as to form a new asymmetric carbon atom; the originally active portion of the molecule is then split off; and if the remainder be active, the problem is solved.

Fischer and Slimmer[1] chose as their starting material the compound helicin which has the formula :—

$$C_6H_{11}O_5.O.C_6H_4.CHO$$

and from the tetracetyl derivative by means of zinc ethyl, they produced the tetracetyl glucoside of *o*-hydroxyphenyl-ethyl-carbinol, which has the constitution :—

$$(CH_3.CO.O)_4.C_6H_7O.C_6H_4.CH(OH).C_2H_5$$

The glucoside itself :—

$$C_6H_{11}O_5.O.C_6H_4.CH(OH).C_2H_5$$

[1] Fischer and Slimmer, *Sitzungsber. K. Acad. Wiss. Berlin*, **1902**, 597; *Ber.*, **36**, 2575 (1903).

was obtained from this by the action of baryta water; and from it in turn, by hydrolysis with very dilute sulphuric acid, glucose, and *o*-hydroxyphenyl-ethyl-carbinol:—

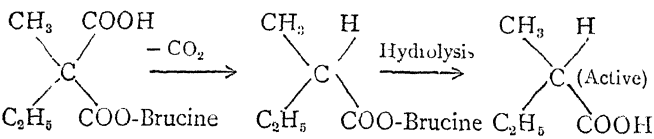
$$HO.C_6H_4.CH(OH).C_2H_5$$

were formed. The latter was, however, found to be inactive.

Cohen and Whitely[1] attempted to solve the problem by esterifying inactive acids with active alcohols, and then treating them in such a way as to produce a new asymmetric carbon atom in the final product after splitting off the active alcohol. For example, they began by esterifying mesaconic acid with menthol, then reduced the ester, and finally hydrolysed it. The resulting methyl-succinic acid was, however, inactive.

Scholtz[2] attempted to form optically active quaternary bases by the action of the active halogen alkyls upon racemic bases; but in this case also no positive results were obtained.

Marckwald[3] found that on heating the acid brucine salt of methyl-ethyl-malonic acid until no more carbon dioxide is evolved, the valeric acid which can be liberated from the substance contains a certain excess of the lævo-isomer. This appears to be a true asymmetric synthesis. The process may be expressed as follows:—



McKenzie[4] has shown that when lævo-menthyl-benzoyl formate, (I.), is treated successively with magnesium-methyl-iodide, water, and acid, it yields a mixture of externally compensated and lævo-methyl-phenyl-glycollic acid, (II.). Thus the production of an asymmetric carbon atom in the acidic part of the molecule of lævo-menthyl-benzoyl formate

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[1] Cohen and Whitely, *Proc.*, **16**, 212 (1900).
[2] Scholtz, *Ber.*, **34**, 3015 (1901).
[3] Marckwald, *Ber.*, **37**, 4696 (1904).
[4] McKenzie, *Trans.*, **85**, 1249 (1904).

is so much influenced by the presence of the active menthyl group that it becomes active.

$$C_6H_5—CO—COOC_{10}H_{19} \qquad\qquad C_6H_5—\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle OH}{|}}{C}}}—COOH$$

(I.) (II.)

McKenzie[1] proved also that when benzoyl-formic lævo-menthyl ester is reduced by means of aluminium amalgam, it yields a mandelic lævo-menthyl ester, $C_6H_5.CH(OH).COOC_{10}H_{19}$, which was found to be a mixture of *d*-mandelic-*l*-menthyl ester with *l*-mandelic-*l*-menthyl ester. Since the latter slightly preponderated in the mixture, the synthesis of the mandelic acid was an asymmetric one. McKenzie[2] has applied this method to other compounds.

The same author[3] applied a similar reaction in the case of the lævo-menthyl ester of pyruvic acid, (I.), which he reduced to the ester of lactic acid, (II.). In this case also a slight excess of the lævo-isomer was present in the final product.

$$CH_3—CO—COOC_{10}H_{19} \qquad\qquad CH_3—CH(OH)—COOC_{10}H_{19}$$

(I.) (II.)

McKenzie and Thompson[4] esterified a number of racemic acids with lævo-menthol and lævo-borneol, and subsequently subjected the esters to partial hydrolysis with an insufficient quantity of alkali. It was found that in some cases this method led to a resolution of the racemic acid.

B. Active Isomers which are not Antipodes.

§ 1. *THEORETICAL.*

In those compounds which we have considered in the preceding pages, we have had to deal with isomers which

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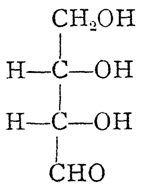
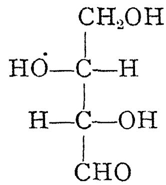
[1] McKenzie, *Trans.*, **85**, 1249 (1904).
[2] McKenzie, *ibid.*, **89**, 365 (1906).
[3] McKenzie, *ibid.*, **87**, 1373 (1905).
[4] McKenzie and Thompson, *Trans.*, **87**, 1004 (1905).

possessed equal and opposite rotatory power, and whose configurations were to one another as object and mirror-image. In the present class the isomers possess neither of these properties. For example, if we consider the two classes of threoses and erythroses, we shall find that their configurations are :—



l-Erythrose.



l-Threose.

which are not mirror-images of one another. When the two formulæ are superimposed, it can be seen that while the group $-$CHOH.CHO is the same in both, the rest of the molecule is different. If we suppose that the group $CH_2OH.CHOH-$ has a rotation value of A, while the other part of the molecule $-$CHOH.CHO has a value B, we shall see that in the two compounds the value of B has always the same sign, *i.e.* the plane of polarization is always turned in the same direction by that group; but that A is $(+)$ in the case of the erythrose, and $(-)$ in the case of the threose, where the atoms are arranged in the opposite direction around the asymmetric carbon atom. Hence the molecule of erythrose will have a rotatory power of $(+A\ +B)$, while in the threose it will be $(-A\ +B)$, and since B is not zero, these two values cannot be equal and opposite.

§ II. *PROPERTIES OF THESE ISOMERS.*

In order to illustrate the differences in properties brought about by the differences in configuration between isomers of this class, it will be best to give a definite example. The case of the aldohexoses may be chosen. The general formula for this class is $CH_2OH.CHOH.CHOH.CHOH.CHOH.CHO$;

and there are six different derivatives—glucose, gulose, mannose, idose, galactose, and talose. The following table exhibits some of their properties. Idose and talose are omitted, as very little is known about them.

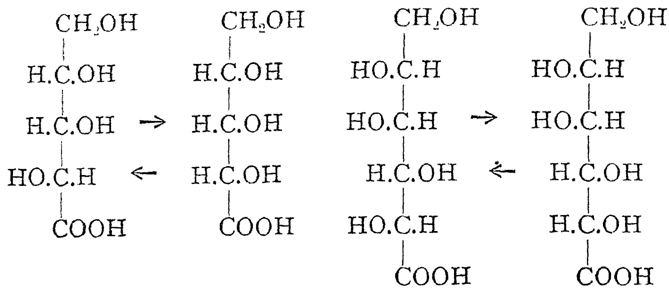
	Glucose.	Gulose.	Mannose.	Galactose.
Rotation . .	±51-6[1]	?	±13-4[2]	±77-85[3]
Sugar : M.P. . .	80-6° ?	syrup	136°	168°
Oxime : M.P. .	136-7°	?	176-184°	175-6°
Hydrazone : M.P.	113-5°	143°	195°	158°

The solubilities and heats of combustion of the isomers are also different from one another.

§ III. *THE TRANSMUTATION OF ACTIVE ISOMERS INTO THOSE OF DIFFERENT CONFIGURATION.*

Fischer discovered this class of reaction[4] in the acids of the sugar group. On heating these acids alone to about 150° C., lactones are formed; but if this be prevented by the presence of such bases as pyridine or quinoline, a change of position of the hydrogen and hydroxyl group attached to the same carbon atom as the carboxyl group occurs. The reaction is reversible, so that the change is never complete, and a mixture of the two configurations results. The cases of the conversion of *l*-arabonic acid into *l*-ribonic, and of *d*-gluconic into *d*-mannonic acid, may be formulated :—

[1] Tollens, *Ber.*, **9**, 487, 1531 (1876); **17**, 2234 (1884).
[2] Fischer and Hirschberger, *Ber.*, **22**, 365 (1889).
[3] Rindell, *Scheibler's N.Z. Rbz. Ind.*, **4**, 170 (1878); Meissl, *J. pr. Chem.*, [2] **22**, 97 (1880).
[4] Fischer, *Ber.*, **23**, 799 (1890); **24**, 2137, 3622, 4215 (1891); **27**, 3193 (1894).



l-Arabonic acid. *l*-Ribonic acid. *d*-Gluconic acid. *d*-Mannonic acid.

§ IV. *PARTIAL RACEMISATION.*

In studying the properties of the quinine salts of methyl-succinic acid, Ladenburg found [1] that when alcoholic solutions were allowed to crystallize at 0°, 18°, and 30° C., a salt was obtained which yielded an inactive acid and had a melting-point 174–5° C.; while the salt of the *d*-acid melts at 169–71° C. Further, he observed the following solubility relations:—

3·2 parts of the	*i*-salt dissolved in	100 parts of	alcohol.
4·2 " "	*d*-salt "	"	"
15 parts approx. of the	*l*-salt "	"	"

From these relations Ladenburg deduces that the inactive salt is not a mixture of the two *d*- and *l*-salts, but is an actual compound; and that the case is one of *partial racemisation*. If the temperature of crystallization be raised to 70° C., a new salt crystallizes out, which shows weak dextro-rotation; this appears to show that the transition temperature lies near 70° C. Pope and Peachey [2] have shown that similar results can be obtained with the tetrahydro-papaverine salt of tartaric acid.

On the other hand, when *d*-gluconic and *l*-mannonic acids are mixed, though the parts of the configuration formulæ

[1] Ladenburg, *Ber.*, **31**, 524 (1898).

[2] Pope and Peachey, *Zeit. Kryst. Min.*, **31**, 11 (1899).

printed in italics are mirror-images of each other, Fischer[1] has found that no pseudo-racemic compound is formed:—

d-Gluconic acid.	l-Mannonic acid.
COOH	COOH
H.OH	H.OH
HO.H	*H.OH*
H.OH	*HO.H*
H.OH	*HO.H*
CH_2OH	*CH_2OH*

Liebermann[2] has observed a somewhat similar case in the dibromides of cinnamic and allocinnamic acids; and Aschan[3] found that the oppositely rotating forms of camphoric and iso-camphoric acid do not unite to form a racemic compound.

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1 Fischer, *Ber.*, **27**, 3226 (1894).
2 Liebermann, *Ber.*, **27**, 2045 (1894).
3 Aschan, *Ber.*, **27**, 2001 (1894).

CHAPTER IV.

THE DETERMINATION OF CONFIGURATION.

§ I. *RELATIVE AND ABSOLUTE DETERMINATION.*

In the present chapter no attempt need be made to show the method of determining the configuration of many carbohydrate derivatives. It will be sufficient to explain how the configurations of the most important sugars have been ascertained; since from them those of the derivatives can easily be deduced. For this reason the following pages deal almost exclusively with the aldoses.

When we speak of determining the configuration of a compound, we do not imply that we intend to establish the *absolute* positions in space of the various atoms in the molecule, but merely their positions in relation to a certain arbitrary standard. For instance, the two active tartaric acids may be represented by the formulæ :—

```
   COOH          COOH
HO.H            H.OH
  H.OH        HO.H
   COOH          COOH
```

It is impossible to determine which of these two formulæ actually represents the tartaric acid which rotates the plane of polarization to the right: all that we can say is that if one formula be chosen to represent the *d*-acid, the other, being its mirror-image, must represent the *l*-compound. Hence the

configuration of the *l*-acid is merely determined with reference to the arbitrary standard which we have set up in choosing the first formula to represent the *d*-acid. Such a method is termed a *relative configuration determination*, not an *absolute* one. The work of Fischer[1] should be consulted.

§ II. *THE PENTOSES.*

When the compounds of the general formula :—

$$CH_2OH.(CH.OH)_3.CHO$$

are considered, it will be found that there are eight possible stereochemical formulæ, corresponding to the *d*- and *l*-forms of arabinose, lyxose, ribose, and xylose.

CH_2OH	CH_2OH	CH_2OH	CH_2OH
HO.H	HO.H	H.OH	H.OH
HO.H	HO.H	HO.H	HO.H
HO.H	H.OH	H.OH	HO.H
CHO	CHO	CHO	CHO
(1)	(2)	(3)	(4)

CH_2OH	CH_2OH	CH_2OH	CH_2OH
H.OH	H.OH	HO.H	HO.H
H.OH	H.OH	H.OH	H.OH
H.OH	HO.H	HO.H	H.OH
CHO	CHO	CHO	CHO
(5)	(6)	(7)	(8)

It will be noticed that (5), (6), (7), and (8) are merely mirror-images of (1), (2), (3), and (4). They may therefore be left out of consideration for the present, since it will be

[1] Fischer, *Ber.*, **27**, 3189 (1894).

easy to name them as soon as the first four substances have been identified.

From the fact that arabinose and ribose give the same osazone, it will be evident that the only difference between these sugars must be in the configuration of the asymmetric carbon atom next to the aldehyde group, since the asymmetry of this atom only is destroyed by the formation of the osazone. Arabinose and ribose must therefore be either (1) and (2) or (3) and (4), for only these pairs have the three upper carbon atoms of each pair alike.

Arabinose on oxidation, yields *active* trihydroxy-glutaric acid, while ribose and xylose produce *inactive* trihydroxy-glutaric acid.

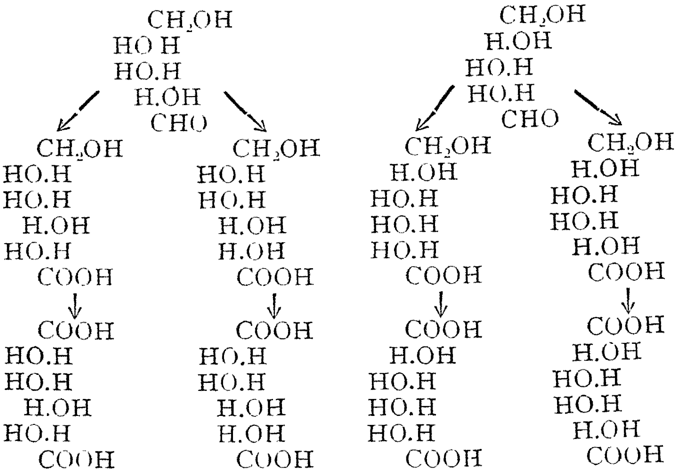
CH_2OH	CH_2OH	CH_2OH	CH_2OH
HO.H	HO.H	H.OH	H.OH
HO.H	HO.H	HO.H	HO.H
HO.H	H.OH	H.OH	HO.H
CHO	CHO	CHO	CHO
↓	↓	↓	↓
COOH	COOH	COOH	COOH
HO.H	HO.H	H.OH	H.OH
HO.H	HO.H	HO.H	HO.H
HO.H	H.OH	H.OH	HO.H
COOH	COOH	COOH	COOH
Inactive.	Active.	Inactive.	Active.
(1)	(2)	(3)	(4)

Therefore ribose and xylose are (1) or (3); arabinose is either (2) or (4); and lyxose, the remaining sugar of the group, must have whichever of the formulæ (2) and (4) is not appropriated to arabinose.

Now, the osazone evidence shows that if arabinose is (2), ribose must be (1); or if arabinose is (4), then ribose must be (3).

When subjected to Kiliani's reaction * and subsequent oxidation, arabinose is found to give two *active* dicarboxylic

acids; while lyxose gives *one active* and *one inactive* dicarboxylic acid.



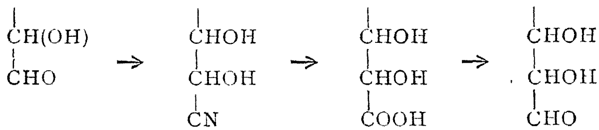
Active. Active. Active. Inactive.

(2) (4)

Arabinose is therefore (2), whence ribose must be (1); and since from the above also, lyxose is (4), xylose must be (3).

---

* Kiliani's reaction[1] consists in (i.) the addition of hydrocyanic acid to the —CHO group of an aldose; (ii.) the hydrolysis of the cyanhydrin thus obtained; (iii.) the reduction of the resulting carboxylic acid with sodium amalgam.



(I.) (II.) (III.)

As can be seen from the above formulæ, it is a method by which a chain may be lengthened to the extent of one carbon atom.

[1] Kiliani, *Ber.*, **19**, 1914, 3033 (1886); **21**, 916 (1888).

The following formulæ have thus been established :—

The riboses.	The arabinoses.	The xyloses.	The lyxoses.
CH_2OH	CH_2OH	CH_2OH	CH_2OH
HO.H	HO.H	H.OH	H.OH
HO.H	HO.H	HO.H	HO.H
HO.H	H.OH	H.OH	HO.H
CHO	CHO	CHO	CHO
(1)	(2)	(3)	(4)

CH_2OH	CH_2OH	CH_2OH	CH_2OH
H.OH	H.OH	HO.H	HO.H
H.OH	H.OH	H.OH	H.OH
H.OH	HO.H	HO.H	H.OH
CHO	CHO	CHO	CHO
(5)	(6)	(7)	(8)

§ III. *THE HEXOSES.*

There are sixteen possible stereochemical forms of compounds having the formula $CH_2OH.(CHOH)_4.CHO$. They are given in the table at the end of this chapter. As in the case of the pentoses, certain of the formulæ represent the mirror-images of the others; so that for the present we need only consider the first eight configurations.

When arabinose is subjected to Kiliani's reaction, and the product is reduced, it yields a mixture of mannose and glucose.

CH_2OH		CH_2OH		CH_2OH
HO.H		HO.H		HO.H
HO.H	←	HO.H	→	HO.H
H.OH		H.OH		H.OH
HO.H		CHO		H.OH
CHO				CHO
(III.)		Arabinose.		(VI.)

Glucose and mannose must therefore be either (III.) or (VI.). Now, it is found that saccharic acid,
COOH—CH(OH)—CH(OH)—CH(OH)—CH(OH)—COOH,
which is obtained by oxidising glucose, can also be produced

by the oxidation of another sugar, gulose. This can occur only if, when the groups —CHO and CH_2OH are transposed in glucose, a new sugar is formed. If this transposition be carried out in formula (III.), we do actually find that a new sugar is produced; which does not occur in the case of the symmetrical formula (VI.).

$$\begin{array}{c} CH_2OH \\ HO.H \\ HO.H \\ H.OH \\ HO.H \\ CHO \\ \text{(III.)} \end{array} \xrightarrow{\text{Transposition}} \begin{array}{c} CHO \\ HO.H \\ HO.H \\ H.OH \\ HO.H \\ CH_2OH \\ \text{New sugar.} \end{array} \qquad \begin{array}{c} CH_2OH \\ HO.H \\ HO.H \\ H.OH \\ H.OH \\ CHO \\ \text{(VI.)} \end{array} \xrightarrow{\text{Transposition}} \begin{array}{c} CHO \\ HO.H \\ HO.H \\ H.OH \\ H.OH \\ CH_2OH \\ \text{Same sugar.} \end{array}$$

Hence glucose is (III.) and mannose is (VI.); and, further the stereo-formula for gulose must be (IV.) :—

$$\begin{array}{c} CH_2OH \\ H.OH \\ HO.H \\ H.OH \\ H.OH \\ CHO \end{array}$$

The case of idose and gulose must next be dealt with. These two sugars give the same osazone; and a mixture of them is produced from xylose by Kiliani's reaction and subsequent reduction. Idose and gulose, therefore, differ only in the configuration of the carbon atoms next their aldehydic groups. But it has already been proved that gulose is (IV.), so that idose must be (VIII.) :—

$$\begin{array}{c} CH_2OH \\ H.OH \\ HO.H \\ H.OH \\ H.OH \\ CHO \\ \text{(IV.)} \end{array} \qquad\qquad \begin{array}{c} CH_2OH \\ H.OH \\ HO.H \\ H.OH \\ HO.H \\ CHO \\ \text{(VIII.)} \end{array}$$

There now remain four formulæ whose identities have not been determined. They are—

(I.)	(II.)	(V.)	(VII.)
CH_2OH	CH_2OH	CH_2OH	CH_2OH
HO.H	HO.H	HO.H	HO.H
HO.H	HO.H	H.OH	H.OH
HO.H	HO.H	H.OH	H.OH
HO.H	H.OH	H.OH	HO.H
CHO	CHO	CHO	CHO

Now, on oxidation or reduction, galactose gives inactive products. It must therefore be either (I.) or (VII.); it cannot be either of the other two.

By Kiliani's reaction, galactose gives two heptonic acids which can be oxidised to *two active* penta-hydroxypimelic acids. Only formula (VII.) fulfils this condition, since formula (I.) gives one active and one inactive acid :—

(I.)	(VII.)
CH_2OH	CH_2OH
HO.H	HO.H
HO.H	H.OH
HO.H	H.OH
HO.H	HO.H
CHO	CHO

CH_2OH	CH_2OH	CH_2OH	CH_2OH
HO.H	HO.H	HO.H	HO.H
HO.H	HO.H	H.OH	H.OH
HO.H	HO.H	H.OH	H.OH
HO.H	HO.H	HO.H	HO.H
HO.H	H.OH	HO.H	H.OH
COOH	COOH	COOH	COOH
↓	↓	↓	↓
COOH	COOH	COOH	COOH
HO.H	HO.H	HO.H	HO.H
HO.H	HO.H	H.OH	H.OH
HO.H	HO.H	H.OH	H.OH
HO.H	HO.H	HO.H	HO.H
HO.H	H.OH	HO.H	H.OH
COOH	COOH	COOH	COOH
Inactive.	Active.	Active.	Active.

(I.) (VII.)

The formula for galactose is therefore (VII.) :—

$$\begin{array}{c} CH_2OH \\ HO.H \\ H.OH \\ H.OH \\ HO.H \\ CHO \end{array}$$

Now, galactose and talose give the same osazone; therefore they differ only in the symmetry of the carbon atom next the aldehyde group. Hence talose must be (V.) :—

$$\begin{array}{c} CH_2OH \\ HO.H \\ H.OH \\ H.OH \\ H.OH \\ CHO \end{array}$$

The sugars corresponding to the remaining two formulæ (I.) and (II.) are not known.

From the results of other reactions, which it is not necessary to discuss here, Fischer has deduced that a close relationship exists between the pentose configurations numbered (**1**), (**2**), (**3**), (**8**), and the hexose formulæ (I.) to (VIII.). Since it is impossible to say which of the two glucose formulæ represents the actual dispositions of the atoms in *d*-glucose, all that can be done is to attribute arbitrarily one of the two formulæ to *d*-glucose, and the mirror-image formula to *l*-glucose. The recognized convention is to choose formula (III.) for *d*-glucose, whence it follows that (XI.) is *l*-glucose. If this nomenclature be adopted, all the hexoses (I.) to (VIII.) are classed as *d*-compounds, while their mirror-images (IX.) to (XVI.) are called *l*-compounds. Similarly, the pentoses (**1**), (**2**), (**3**), (**8**), since they are related to the *d*-hexoses, are also called *d*-compounds. Thus the configurations of all the pentoses and hexoses have been settled.

§ IV. *THE HEPTOSES.*

When *d*-glucose is treated by Kiliani's reaction, two acids are formed: α-glucoheptonic acid, and β-glucoheptonic acid.

On oxidation, α-glucoheptonic acid gives an *active* acid, while the β-acid yields an *inactive* product. Therefore (I.) represents α-glucoheptonic acid, and (II.) the β-compound.

CH_2OH
HO.H
HO.H
H.OH
HO.H
CHO
Glucose.

(I.)	(II.)
CH_2OH	CH_2OH
HO.H	HO.H
HO.H	HO.H
H.OH	H.OH
HO.H	HO.H
H.OH	HO.H
COOH	COOH
α-Glucoheptonic acid.	β-Glucoheptonic acid.
↓	↓
COOH	COOH
HO.H	HO.H
HO.H	HO.H
H.OH	H.OH
HO.H	HO.H
H.OH	HO.H
COOH	COOH
(Active)	(Inactive)

§ V. *THE TETROSES.*

There are four possible configurations for a compound of the general formula $CH_2OH—CH(OH)—CH(OH)—CHO$, viz. :—

CH_2OH	CH_2OH	CH_2OH	CH_2OH
H.OH	HO.H	HO.H	H.OH
H.OH	H.OH	HO.H	HO.H
CHO	CHO	CHO	CHO
(a)	(b)	(c)	(d)

Of these, (c) and (d) are the mirror-images of (a) and (b).

When *l*-xylose is treated by Wohl's reaction,* it is converted into *l*-threose,[1] which, on oxidation, forms *l*-tartaric acid :—

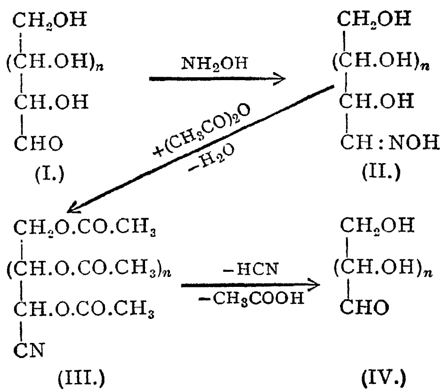
l-Xylose.		*l*-Threose.		*l*-Tartaric acid.
CH_2OH		CH_2OH		COOH
HO.H		HO.H		HO.H
H.OH	→	H.OH	→	H.OH
HO.H		CHO		COOH
CHO				

Hence, *d*-threose and *d*-tartaric acid are :—

CH_2OH	COOH
H.OH	H.OH
HO.H	HO.H
CHO	COOH

Wohl's reaction, when applied to *l*-arabinose, produces

* Wohl's reaction (*Ber.*, **32**, 3666, 1899) may be expressed as follows :—



The oxime (II.) is made in the usual way ; it is then allowed to react with acetic anhydride and sodium acetate, whereby water is lost and the nitrile (III.) is formed. This is treated with caustic potash and then with hydrochloric acid, whereby acetic acid and hydrocyanic acid are liberated in turn, and the aldehyde (IV.) is formed.

[1] Maquenne, *Bull Soc. chim.*, [3] **23**, 1587 (1900).

l-erythrose, whose formula must therefore be that shown below :—

$$\begin{array}{c} CH_2OH \\ H.OH \\ H.OH \\ HO.H \\ CHO \\ \textit{l}\text{-Arabinose.} \end{array} \longrightarrow \begin{array}{c} CH_2OH \\ H.OH \\ H.OH \\ CHO \\ \textit{l}\text{-Erythrose.} \end{array}$$

Hence, *d*-erythrose is :—

$$\begin{array}{c} CH_2OH \\ HO.H \\ HO.H \\ CHO \end{array}$$

§ VI. *COMPOUNDS CONTAINING ONE ASYMMETRIC CARBON ATOM*

When *d*-tartaric acid is reduced with hydriodic acid, it yields *d*-malic acid[1] :—

$$\begin{array}{c} COOH \\ H.OH \\ HO.H \\ COOH \\ \textit{d}\text{-Tartaric acid} \end{array} \longrightarrow \begin{array}{c} COOH \\ CH_2 \\ HO.H \\ COOH \\ \textit{d}\text{-Malic acid} \end{array}$$

Hence, *l*-malic acid is :—

$$\begin{array}{c} COOH \\ CH_2 \\ H.OH \\ COOH \end{array}$$

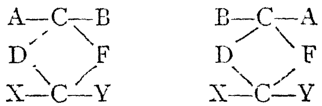
---

[1] Schmitt, *Annalen*, **114**, 106 (1860).

CHAPTER V.

THE ASYMMETRIC CARBON ATOM AS A RING-MEMBER.*

WHEN an asymmetric carbon atom is introduced into a ring, it will at once be seen that the existence of two antipodes will depend upon the positions of certain atoms with regard to the ring itself. For instance, in the case of the two compounds shown below, it is obvious that the one isomer is produced from the other by exchanging the groups A and B :—



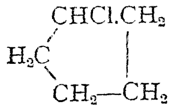
This introduces the conception of cis-trans isomerism in rings, which will be dealt with fully in another part of this book. In the present chapter the matter will be considered only in so far as it concerns the production of optical activity in these compounds.

§ I. *THE GRAPHIC REPRESENTATION OF STEREO-ISOMERS OF THE CYCLIC TYPE.*

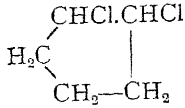
It is evident that if, in any cyclic molecule, the plane of the ring is a plane of symmetry of the molecule, neither optical activity nor geometrical isomerism is to be expected. In order to render the differentiation of stereoisomeric bodies simple, Aschan[1] has devised the following method. He represents the plane of the ring by a straight line, so that in saturated alicyclic compounds the substituents must lie either above or below this line. For instance, mono-chloro- and cis-dichloro-pentamethylene are represented as shown below :—

* The first chapter of Part II. should be consulted.

[1] Aschan, *Ber.*, **35**, 3390 (1902).

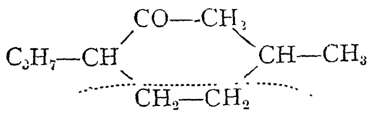


Cl



Cl Cl

The substituents are counted clockwise. It is not usually necessary to indicate an unsubstituted methylene group; but if two substituents be symmetrically placed with regard to the molecule as a whole, while a third is placed unsymmetrically with regard to the first two, it is necessary to represent a methylene group. This is usually done by means of a vertical line. To make this point clear, the case of menthone may be shown. Its molecule contains two unlike substituents—isopropyl (X) and methyl (Y)—in symmetrical positions, while an oxygen atom is attached to a third carbon atom. The oxygen atom (ZZ), being attached to two carbon valencies, must be represented as both above and below the plane of symmetry of the molecule, since if it were replaced by two hydrogen atoms one would be above and the other below this plane. The formulæ show that four space formulæ, all active, are possible, (I.) and (III.) being mirror images of (II.) and (IV). :—

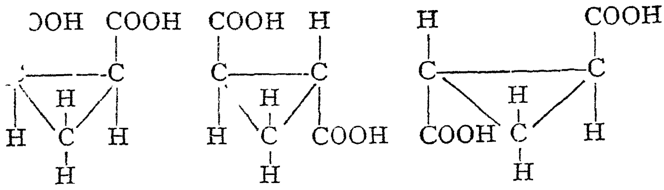


Unrepresented in formulæ.

XZ|Y	Y|ZX	XZ|	|ZX
Z|	|Z	Z|Y	Y|Z
(I.)	(II.)	(III.)	(IV.)

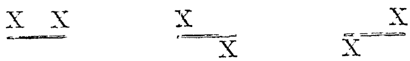
It should be noticed that only those monocyclic forms are identical which can be superposed either directly or after turning the paper through an angle of 180°.

For example, the 1,2-dicarboxylic acids of trimethylene exist in the forms represented by the three formulæ below; (this excludes the racemic form):—



(I.) (II.) (III.)

These are represented, on Aschan's system, by the following figures :—



(I.) (II.) (III.)

It can be seen at once from either the first or second series of formulæ that (I.) has a plane of symmetry perpendicular to the plane of the paper and lying between the two X's. It therefore represents an internally compensated active form. On the other hand, (II.) and (III.) are mirror-images of each other, and represent the two active forms of the acid. The racemic form would be obtained by mixing (II.) and (III.) in equimolecular proportions.

§ II. *CYCLIC COMPOUNDS WITH ONE OR MORE ASYMMETRIC CARBON ATOMS IN THE RING.*

Cyclic compounds with one asymmetric carbon atom in the ring exist in two isomeric active forms, which are optical antipodes of one another. They differ in no great degree from ordinary open-chain antipodes, and therefore need not be discussed in detail.

We must now deal with compounds with more than one asymmetric carbon atom in the ring; and it will be best to examine first the monocyclic substances. A close resemblance can be traced between this class of compounds and those of the aliphatic series, which contain more than one asymmetric carbon atom. Just as in the case of the tetroses, a cyclic compound containing two asymmetric carbon atoms in the

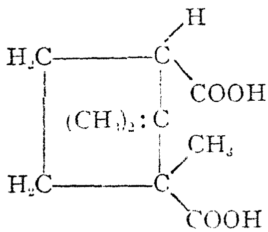
ring can exist in four optical isomers, divisible into two pairs of antipodes. In general, however, the differences between two open-chain antipodes are less marked than those between cyclic antipodes; and this distinction is usually attributed to the existence in aliphatic compounds of free rotation of the carbon atoms about a common axis, which tends to make one isomer more like the other in such properties as anhydride-formation; for since freedom of this kind does not exist in the cyclic isomers, they cannot be expected to show the same resemblances.

In the case where we have two asymmetric carbon atoms as members of the ring in a cyclic compound, we may have one of two alternatives; the two asymmetric atoms may be structurally different, or they may be alike in structure. Only a few examples of the first type are known in which it has been possible to isolate all four active isomeric forms. The formulæ of all the isomeric camphoric acids may be given as an example. For information, reference may be made to the papers on *d*-camphoric acid,[1] on *l*-camphoric acid,[2] on *d*-isocamphoric

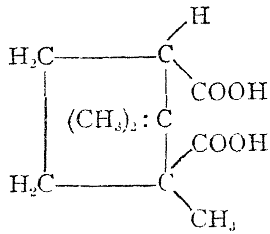
[1] Kosegarten, *Dissertatio die Camphora et partibus qui eam constituunt* (1785); Malaguti, Liebig, and Laurent, *Annalen*, **22**, 38, 50, 135 (1837); Gerhardt and Lies-Bodart, *Annalen*, **72**, 293 (1849); Moitessier, *Annalen*, **120**, 252 (1861); Hlasiwetz and Grabowsky, *Annalen*, **145**, 205 (1868); V. Meyer, *Ber.*, **3**, 117 (1870); Wreden, *Annalen*, **163**, 323 (1872); Kachler, *Annalen*, **191**, 143 (1878); Montgolfier, *Ann. Chim. Phys.*, [5] **14**, 5 (1878); Maissen, *Gazzetta*, **10**, 280 (1880); Schroeder, *Ber.*, **13**, 1072 (1880); Ballo, *Ber.*, **14**, 335 (1881); Kannonikow, *J. pr. Chem.*, [2] **31**, 349 (1885); Berthelot, *Bull. Soc. chim.*, [2] **45**, 70 (1886); Haller, *Compt. rend.*, **104**, 68 (1887); Gal and Werner, *Bull. Soc. chim.*, [2] **47**, 163 (1887); Hartmann, *Ber.*, **21**, 221 (1888); Manning and Edwards, *Am. Chem. J.*, **10**, 233 (1888); Louguinine, *Compt. rend.*, **107**, 624 (1889); Ostwald, *Zeit. physikal. Chem.*, **3**, 404 (1889); Jungfleisch, *Compt. rend.*, **110**, 791 (1890); Bruhl, *Ber.*, **24**, 3409 (1891); Friedel, *Compt. rend.*, **113**, 825 (1891); Gladstone, *Trans.*, **59**, 590 (1891); Bruhl and Braunschweig, *Ber.*, **25**, 1802 (1892); Osann, *Ber.*, **25**, 1808 (1892); Noyes, *Am. Chem. J.*, **16**, 501 (1894); Aschan, *Ber.*, **27**, 2001 (1894); *Acta Soc. Scient. Fennicæ*, **21**, [5], 47 (1895); Krafft and Weinlandt, *Ber.*, **29**, 2241 (1896); Vanino and Thiele, *Ber.*, **29**, 1728 (1896); Walden, *Ber.*, **29**, 1700 (1896); Étard, *Compt. rend.*, **130**, 570 (1900); Aschan, *Annalen*, 316, 209 (1901); Komppa, *Ber.*, **36**, 4332 (1903).

[2] Chautard, *Compt rend.*, **56**, 698 (1863); Louguinine, *Compt. rend.*, **107**, 624 (1888); Jungfleisch, *Compt. rend.*, **110**, 791 (1890).

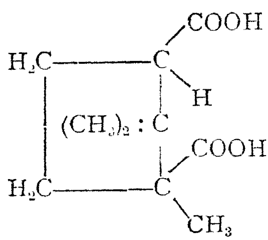
acid,[1] and on *l*-isocamphoric acid.[2] Arbitrarily choosing one configuration to represent the dextro-camphoric acid, we may write all four isomers thus :—



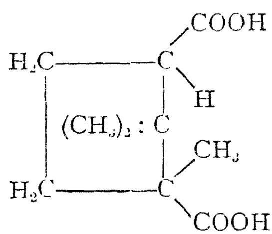
d-Camphoric acid.



l-Isocamphoric acid.



l-Camphoric acid.



d-Isocamphoric acid.

Three other examples may be mentioned—limonene nitrosochloride,[3] limonene nitrolanilide,[4] limonene nitrolpiperide,[5] and α-phenyl-α'-methyl-piperidine.[6] The material at present at our command, however, is so restricted that it is hardly worth while to enter into a discussion of these compounds.

[1] Jungfleisch, *Compt. rend.*, **110**, 792 (1890); Aschan, *Acta Soc. Scient. Fennicæ*, **21**, [5] 53, 164 (1895).

[2] Wreden, *Annalen*, **163**, 328 (1872); Kachler, *Annalen*, **191**, 146 (1878); Friedel, *Compt. rend.*, **108**, 978 (1889); Marsh, *Chem. News*, **60**, 307 (1889); Jungfleisch, *Compt. rend.*, **110**, 792 (1890); Aschan, *Ber.*, **27**, 2001 (1894); Mahla and Tiemann, *Ber.*, **28**, 2153 (1895); Auwers and Schleicher, *Annalen*, **309**, 343 (1900).

[3] Wallach, *Annalen*, **252**, 106 (1889); **270**, 184 (1892); *Ber.*, **28**, 1308, 1474 (1895); Baeyer, *Ber.*, **28**, 648 (1895).

[4] Wallach, *Annalen*, **252**, 118 (1889); **270**, 180 (1892).

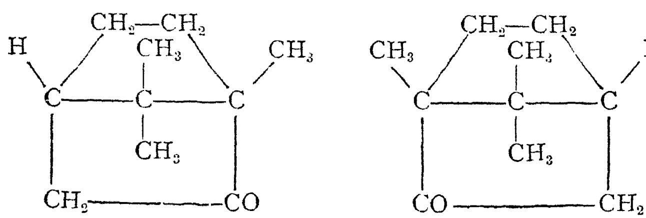
[5] Wallach, *Annalen*, **252**, 113, 146 (1889).

[6] Scholtz and Muller, *Ber.*, **33**, 2842 (1900).

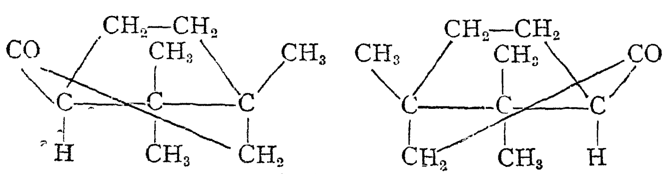
When the two asymmetric carbon atoms in the ring are structurally alike, we have an isomerism resembling that of the tartaric acids: the existence of two active isomers and a single internally compensated one can be foreseen. Here, again, the material known is too restricted to yield any inferences, and the same may be said for the cases in which there are more than two asymmetric carbon atoms in the ring.

In comparison with the number of open-chain stereoisomeric substances, only a few compounds are known which contain a double cyclic system in their molecule. The chief substances of this class are naturally occurring bodies like the terpenes. It will not be necessary to enter into a detailed study of the group; but since in their main characteristics these dicyclic compounds differ to some extent from the substances which have already been described, it is desirable to mention such differences here.

It appears that in some cases where two sets of isomers are to be expected from the graphic formula of a compound, only one of the two sets actually exists; for the other is apparently in too great a state of strain to be stable. For example, in the case of camphor, we might expect to find four compounds corresponding to the four formulæ:—



d- and *l*-Camphor.



(Unknown)

It seems probable that the result of heaping up ring upon ring is to produce a tendency towards grouping the atoms of each ring more or less in a plane configuration.

Certain dicyclic compounds have the second ring in a plane perpendicular to the first, while others have the two planes at different angles; these differences naturally produce variations in the optical behaviour of the bodies in question. The papers by Piccinini,[1] Aschan,[2] and Skraup[3] may be consulted on this subject.

§ III. *INACTIVE MOLECULES WHICH APPARENTLY HAVE NO PLANE OF SYMMETRY.*

To determine whether or not a compound is optically active, it has hitherto been sufficient to see whether or not the space formula of one half of the compound was the mirror-image of that of the other half. If it was, that showed that the compound in question possessed a plane of symmetry, and was therefore inactive. Now, however, we must consider a slightly different case.

Ladenburg[4] was the first to call attention to this phenomenon, which he had observed in the case of α- γ-diacipiperazines :—

```
      /CH.R—CO\
X.N              N.X
      \CO—CH.R/
```

The peculiarity of such molecules lies in the fact that they can be divided by a plane into two halves, one of which must then be turned through an angle of 180° in order to make it the mirror-image of the other half. According to the ordinary view, such a molecule ought to be active, but, as a matter of fact, it is inactive.

---

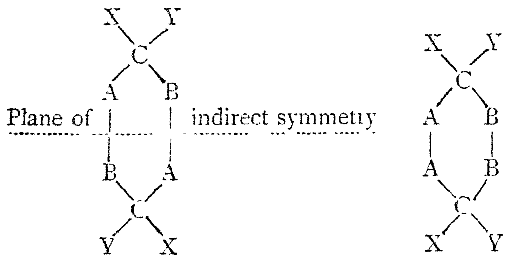
[1] Piccinini, *Gazzetta*, **30**, I. 125 (1900).

[2] Aschan, *Annalen*, **316**, 200 (1901).

[3] Skraup, *Ber.*, **36**, 141 (1903).

[4] Ladenburg, *Ber.*, **28**, 1995, 3104 (1895).

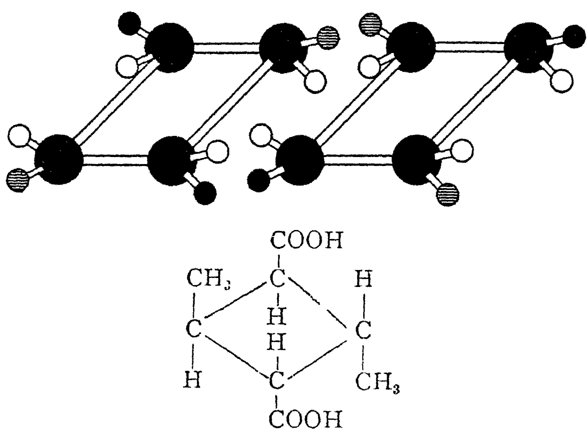
According to Groth,[1] the plane in question is one of *indirect symmetry*. The following figure shows what is meant:—



(I.) (II.)

The lower half of (I.) must be turned through an angle of 180° in order to produce (II.), in which the top half of the molecule is the mirror-image of the lower half.

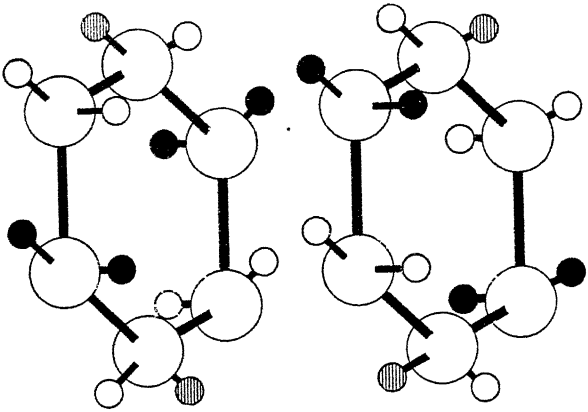
The following instances of this kind may be mentioned: 1,3-dimethyl-cyclobutane-2,4-dicarboxylic acid (Fig. 19); the keto-form of trans-succinylo-succinic acid (Fig. 20); trans-3,6-dimethyl-1,4-cyclohexadiene-1,4-dicarboxylic acid (Fig. 21).

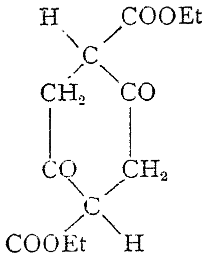


(I.)

FIG. 19.

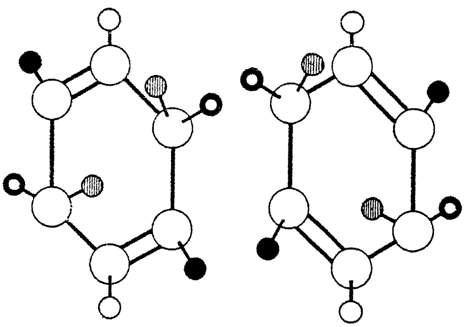
[1] Groth, *Ber.*, **28**, 2510 (1895).

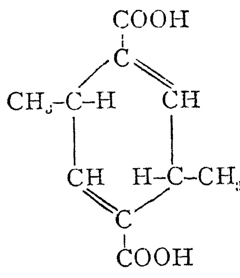




(II.)

FIG. 20.

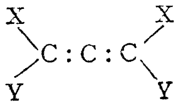




(III.)

FIG. 21.

Hartwall, in his "*Studien über das optische Drehungsvermögen aliphatisch cis-trans-isomerer Verbindungen, nebst Betrachtungen über asymmetrischen Kohlenstoff und Molekulare Asymmetrie*,"[1] has dealt with molecules of the allylene type, and has shown that no plane of indirect symmetry is to be found in compounds of the general formula :—



The figure below illustrates such a case graphically :—

If we draw a plane, *P*, through the middle carbon atom, perpendicular to the line joining the centres of the three carbon atoms, and then revolve one of the halves of the molecule about this axis through an angle of 90°, the plane *P* becomes a plane of symmetry of the molecule. It is not, however, a plane of indirect symmetry, for if the revolution be continued through another 90° (180° in all), no symmetry is then found. The compound should therefore be active, and exist in two antipodes. This had been predicted by van't Hoff in his book, *The Arrangement of Atoms in Space*. A practical application of this is found in compounds of the types :—

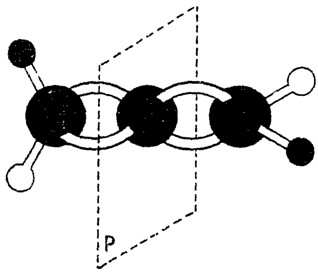
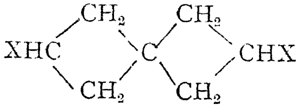
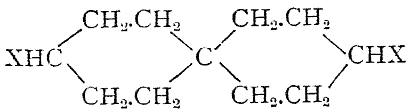


FIG. 22.

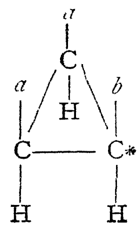


[1] *Dissertation*, Helsingfors, 1904.



Hartwall defines the relation between optical activity and molecular asymmetry as follows: "A compound is optically active when its molecule, represented in tetrahedral models, cannot be brought into a form which possesses one or more planes of symmetry, common or indirect."

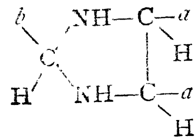
§ IV. *PSEUDO-ASYMMETRY IN CYCLIC COMPOUNDS.*



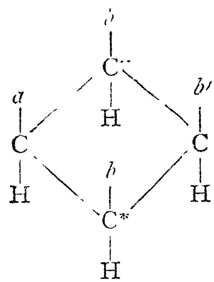
In the above figure, it is obvious that two of the carbon atoms are really asymmetric, while on closer examination it will be found that the one marked with an asterisk is pseudo-asymmetric. This will be made evident if we consider what an observer situated on the pseudo-asymmetric atom would see in each case if he looked along the bonds, first at the carbon atom to his left, and then at the one on his right—

(left hand) (right hand)

Such compounds will therefore occur in four different forms: two active and two inactive; the same phenomenon is to be expected in other ring systems, such as:—



and also in the case of the 2,5-dimethyl-cyclopentane-1, carboxylic acid, by Wislicenus,[1] where all three isomers have been isolated, though the racemic compound has not yet been resolved.



In a compound of the type shown in the figure, the carbon atoms marked with an asterisk are truly asymmetric, and if their asymmetries are opposite to one another the other two carbon atoms will be pseudo-asymmetric. It should be noticed that *b'* may be similar to or different from *b* in structure without making any change in the number of isomers found. From such a compound as this, four intramolecularly compensated and four active isomers are to be expected. Similar instances are to be found in di-cyclic compounds, but in their case the problem is more complicated.

§ V. *RACEMISATION OF CYCLIC ISOMERS.*

The methods which are applicable in the case of open-chain compounds are equally serviceable in the cyclic series.

---

[1] Wislicenus, *Ber.*, **34**, 2572 (1901).

It is unnecessary to enter into great detail on this point; a few examples will suffice.

Heat alone may be used in some cases to convert an active substance into an inactive mixture. For instance, in the course of his researches upon tartaric acid, Pasteur [1] showed that when the cinchonine salt of active tartaric acid was heated for several hours to a temperature of 165–175° C., the cinchonine was to a great extent converted into the stereoisomeric cinchonidine. Marsh [2] found that β-bromo-camphor, when distilled under ordinary pressure, yields α-bromo-camphor.

Heating in a sealed tube with water, acid, or alkali, is sufficient to racemise many active substances. Pospischill [3] showed that cis-pentamethylene-1,3-dicarboxylic acid, when heated with water in a sealed tube to 180° C., was half converted into the trans-variety. Baeyer [4] was able to convert hydromellitic acid into iso-hydromellitic acid by heating it for three hours in a tube with concentrated hydrochloric acid at 150° C. Montgolfier [5] and Haller [6] observed that the stable form of borneol was produced when the labile form was boiled with sodium.

In some cases, the effect of acids and bases alone suffices to convert the one form into the other. The dextro and lævo forms of menthone can thus be racemised.[7]

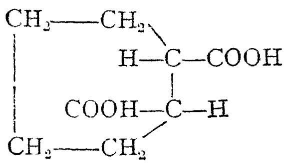
Auto-racemisation has been observed in the case of the menthones, and also with hydromellitic acid, which Baeyer [1] found was changed into iso-hydromellitic acid on standing.

Another method deserves mention. In the case of a trans-dicarboxylic acid which is to be converted into the corresponding cis-compound, it has been found that this can be brought about by converting the trans-acid into an anhydride, from which the cis-acid is obtained by the addition of water in the

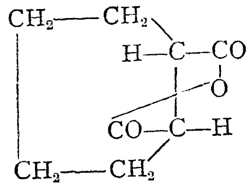
---

[1] Pasteur, *Compt. rend.*, **37**, 162 (1853).
[2] Marsh, *Trans.*, **57**, 82 (1890); **59**, 968 (1891).
[3] Pospischill, *Ber.*, **31**, 1950 (1898).
[4] Baeyer, *Ber.*, **1**, 118 (1868); *Annalen Suppl.*, 7, 15, 43 (1870).
[5] Montgolfier, *Dissertation*, Paris, 1878.
[6] Haller, *Compt. rend.*, **105**, 229 (1887).
[7] Beckmann, *Annalen*, 250, 333, 358 (1889).

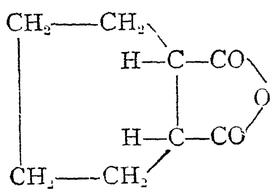
usual way. For example, if we begin with trans-hexahydrophthalic acid (I.), we convert this into the anhydride (II.); this compound, on heating, is changed into the anhydride (III.) of the cis-acid (IV.).



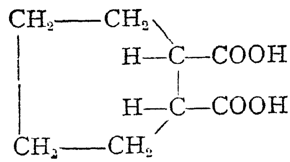
(I.)



(II.)



(III.)



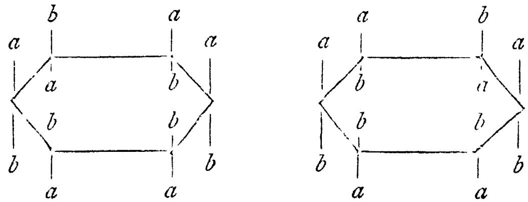
(IV.)

Racemisation in the cyclic compounds may be said to be rarer than in the open-chain series. In the case of mono-cyclic substances it is frequently observed, but it does not often occur in the case of di-cyclic bodies. Whether this difference is due to the hindrance to revolution which chain formation is supposed to exert upon the carbon atoms is at present unknown. It is possible that investigations on this point might throw light upon the actual mechanism of the racemising process.

CHAPTER VI.

TWO EXCEPTIONAL CASES OF OPTICAL ACTIVITY.

In certain cyclic compounds it is possible to imagine a configuration such that the compound and its mirror-image would not be superposable, and yet in which no true asymmetric carbon atom would be present. For example, in a ring compound such as that shown in the figure below, two isomers obviously exist, and yet neither contains an asymmetric carbon atom :—



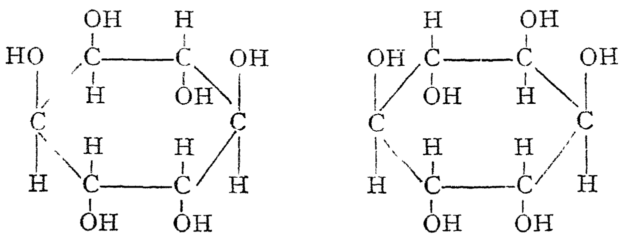
Such a molecule as that shown has no plane of symmetry; and in order to distinguish this case from one in which asymmetry is due to the presence of an asymmetric carbon atom, it is usually described as *molecular asymmetry*. Though apparently the asymmetric carbon atom, as usually understood, is absent in the present instance, this is not really the case; for on closer inspection it will be seen that all six carbon atoms in the above figure are pseudo-asymmetric.

In practice, only one such active type is known, and it is a member of the hexamethylene series. The inosites[1] are

[1] Maquenne, *Ann. Chim. Phys.*, [6] **22**, 264 (1890); *Compt. rend.*, **109**, 812 (1889).

hexa-hydroxy-cyclo-hexanes, which occur naturally as methyl ethers, quebrachite and pinite. A third, inactive, variety also is found in nature, being distinguished from the others in that it is found naturally in the form of the alcohol, and not as an ether.

The space formulæ of the two active inosites are shown below :—



The case of the inosites, though not falling expressly into line with the van't Hoff-Le Bel theory of the asymmetric carbon atom, can yet be construed in a way which is not in contradiction with that conception. It is otherwise with the instance which must now be mentioned; for in this case, apparently, there is no possible chance of agreement between theory and practice.

Ordinary malic acid is known to exist in two optically active forms, which can be represented by the two formulæ :—

COOH	COOH
H.H	H.H
HO.H	H.OH
COOH	COOH

A third isomer, crassulaic malic acid, has been discovered[1] in certain plants (*Bryophyllum colynicum*, *Echeveria secunda glauca*, *Cotyledon*, etc.). Its calcium, barium, and lead salts, methyl ester and amide were studied by Aberson,[2] who also

[1] Meyer, *Landw. Vers. Stat.*, 1878, 298; Schmidt. *Arch. f. Pharm.*, (3) **24**, 535.

[2] Aberson, *Verh. K. Akad. Wetensch. Amsterdam*, 1898; *Ber.*, **31**, 1432 (1898).

determined its molecular weight and basicity. His results proved the structural identity of the acid with common malic acid; but the following table shows the differences between the physical and chemical properties of the two bodies :—

Common Malic Acid.	*Crassulaic Malic Acid.*
Crystalline.	Syrup.
Acid Ca salt easily formed.	Acid Ca salt hard to produce.
,, NH_4 ,, ,,	No acid NH_4 salt.
On esterifying, easily gives fumaric ester.	Does not do so.
Most salts have *d*-rotation.	Most salts have *l*-rotation.
Forms no lactonic anhydride.	Forms one like lactic acid.
On dry distillation, products are fumaric and maleic acids.	Only traces of maleic and fumaric. Chief products are anhydride, CO_2, CO, and CH_3CHO.
Ca salt pptd. crystalline on boiling; does not redissolve on cooling.	Ca salt pptd. amorphous on boiling; redissolves on cooling.

To account for this, it has been supposed that malic acid actually exists in the three configurations shown below; but this does not explain the effects which it produces upon the plane of polarization.

COOH	COOH	COOH
HO.H	HO.H	HO.H
COOH.H	H.COOH	H.H
H	H	COOH

Walden[1] states that the crassulaic acid and the common malic acid differ only in optical properties. Both give strongly active anhydrides of equal lævo-rotatory power. The question of the isomerism is undecided at present.

[1] Walden, *Ber.*, **31**, 2706 (1898).

CHAPTER VII.

THE QUANTITATIVE RELATIONS BETWEEN ACTIVITY AND THE NATURE OF THE ASYMMETRIC CARBON ATOM.

§ I. *GENERAL.*

WHEN we attempt to discover which properties of the asymmetric carbon atom have an influence upon the rotatory power of a compound, the problem appears to be nearly insoluble, as it seems impossible to distinguish between the details which are important, and those which are not. At present the question is in an elementary stage, in spite of the immense amount of research which has been carried out in the past. It has, unfortunately, been the custom to treat the effect of varying one condition as separate from the rest of the subject; and it is probable that little real progress will be made until every known factor is taken into account in each experiment. Winther[1] has attempted to do this in certain cases. In this chapter a few of the more salient points of the subject will be discussed; those chosen being the effect of unsaturation, the influence of ring-formation, the effect of several asymmetric carbon atoms in a compound, rotatory powers of structure isomers, stereoisomers, and of homologous series.

§ II. *ISOMERIC BODIES.*

1. Structural Isomerism in Open Chains.—The facts known in this division are confined to some esters, which can be

[1] Winther, *Zeit. physikal. Chem.*, **55**, 257 (1905); **56**, 703 (1906).

divided into three classes.[1] In the first class the isomerism is produced by the transference of the active radicle from one part of the molecule to another, *e.g.* amyl-acetic acid and amyl acetate. In such cases the difference of rotatory power is very great:—

	$[\alpha]_D$
Amyl-acetic acid ($C_5H_{11}.CH_2.COOH$)	$+ 8{\cdot}53^\circ$
Amyl acetate ($CH_3.COOC_5H_{11}$)	$+ 2{\cdot}50^\circ$

The second class of isomerism is that where the active alcohol remains the same while isomeric acids are employed, *e.g.* active amyl esters of normal- and isobutyric acid. Here the differences in rotation are not very marked:—

	$[\alpha]_D$
Amyl *n*-butyrate ($CH_3.CH_2.CH_2.COOC_5.H_{11}$)	$+ 2{\cdot}97^\circ$
Amyl isobutyrate ($(CH_3)_2CH.COOC_5H_{11}$)	$+ 2{\cdot}83^\circ$

In the third class the active acid remains the same, while isomerism is confined to the inactive alcohol, radical, *e.g.* methyl normal butyl malate, and methyl isobutyl malate. In this case also the differences are small:—

	$[\alpha]_D$
Methyl-*n*-butyl malate	$- 22{\cdot}44^\circ$
Methyl-isobutyl malate	$- 22{\cdot}36^\circ$

2. Structural Isomerism in Benzene Derivatives.—This branch of the subject has been studied by numerous workers;[2]

[1] Walden, *Zeit. physikal. Chem.*, **15**, 636 (1894).

[2] Binz, *Zeit. physikal. Chem.*, **12**, 727 (1893); Goldschmidt and Freund, *Zeit. physikal. Chem.*, **14**, 394 (1894); Frankland and Wharton, *Trans.*, **69**, 1309, 1583 (1896); **75**, 337 (1899); Walden, *Zeit. physikal. Chem.*, **17**, 245 (1895); Guye, *Bull. Soc. chim.*, [3] **15**, 1157 (1895); Frankland and MacCrae, *Trans.*, **73**, 307 (1898); Tschugaeff, *Ber.*, **31**, 1775 (1898); Bijuchonenko, *J. pr. Chem.*, [2] **59**, 45 (1899); Frankland and Aston, *Trans.*, **75**, 493 (1899); **79**, 511 (1901); Frankland, Wharton, and Aston, *Trans.*, **79**, 266 (1901); Cohen and Whitely, *Trans.*, **79**, 1305 (1901); Frankland and Ormerod, *Trans.*, **83**, 1342 (1903); Rupe, *Annalen*, **327**, 157 (1903); Frankland and Slator, *Trans.*, **83**, 1349 (1903); Frankland and Harger, *Trans.*, **83**, 1571 (1903); Briggs and Cohen, *Trans.*, **83**, 1213 (1903); **85**, 1262 (1904); Cohen and Raper, *Trans.*, **85**, 1262, 1271

and it has been established that position-isomerism exerts a considerable influence upon the rotation of these isomers. Frankland and Wharton, studying the methyl and ethyl esters of *o*-, *m*-, and *p*-di-toluyl-tartaric acids, found that the para-derivatives are more active than the meta-, and these in turn more active than the ortho- compounds. The carvoximes and malic esters are exceptions to this rule, as in their case the specific rotation of the *o*-, *m*-, and *p*-substituted bodies increases in the order $o >, m >, p$, instead of $p >, m >, o$.

The following table gives results obtained by Cohen in conjunction with Briggs and Raper:—

Menthyl ester of	Chlorobenzoic	Bromobenzoic	Nitrobenzoic	Benzoic
Temperature	20° C.	20° C.	65° C.	20° C.
Ortho- . .	− 195·0°	− 205·0°	− 381·2°	—
Meta- . .	− 236·9°	− 238·7°	− 251·1°	− 236·3°
Para- . . .	− 237·3°	− 238·8°	− 234·8°	—

3. **Stereoisomerism.**—Walden [1] and Hartwall [2] have carried out a series of investigations on this point, and find that in the case of amyl esters of maleic, chloromaleic, bromomaleic, citraconic, and the corresponding stereoisomeric acids, the fumaroid form has, on the average, a molecular rotation 4·5° higher than the maleinoid form.

Bischoff, Claisen, and Sinclair [3] studied the properties of two hydroxymethylene-camphor benzoates, which Aschan [4] states are stereoisomeric. They found the following results:—

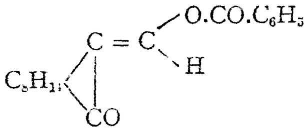
(1904); Urban, *Arch. Pharm.*, **242**, 51 (1904); Cohen and Zortman, *Trans.*, **89**, 47 (1906); Cohen and Armes, *Trans.*, **89**, 454 (1906); Frankland and Twiss, *Trans.*, **89**, 1852 (1906); Frankland and Done, *Trans.*, **89**, 1859 (1906).

[1] Walden, *Zeit. physikal. Chem.*, **15**, 638 (1894); **20**, 377 (1896).

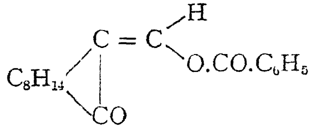
[2] *Dissertation*, Helsingfors, 1904.

[3] Bischoff, Claisen, and Sinclair, *Annalen*, **281**, 331 (1894).

[4] Aschan, *Chemie der Alicyklischen Verbindungen*, p. 296.



$[\alpha]_D = + 139{\cdot}02$



$[\alpha]_D = + 159{\cdot}29$

Wallach[1] has studied the influence of stereoisomerism in the oximes.

§ III. *HOMOLOGOUS SERIES.*

In a series of homologous esters, it appears that in the lower members the increase of CH_2 produces a noticeable effect, sometimes increasing and sometimes decreasing the molecular rotation; but the differences between the members of a series tend to diminish as the molecular weight increases, and in some series there finally comes a point at which the influence is exerted in the opposite direction, so that after that member the rotations of the homologues go through the same changes in the reverse direction.

	$[M]_D$
Amyl formate	$+ 2{\cdot}33°$
Amyl acetate	$+ 3{\cdot}29°$
Amyl propionate	$+ 3{\cdot}99°$
Amyl *n*-butyrate	$+ 4{\cdot}25°$
Amyl *n*-valerate	$+ 4{\cdot}33°$
Amyl *n*-caproate	$+ 4{\cdot}46°$
Amyl *n*-heptylate	$+ 4{\cdot}42°$
Amyl *n*-caprylate	$+ 4{\cdot}49°$
Amyl *n*-nonylate	$+ 4{\cdot}44°$
Amyl laurate	$+ 4{\cdot}21°$
Amyl palmitate	$+ 4{\cdot}17°$

Forster,[2] studying the homologues of bornylamine, found the following figures:—

[1] Wallach, *Annalen*, **332**, 337 (1904).
[2] Forster, *Trans.*, **75**, 934 (1899).

	$[\alpha]_D$	$[M]_D$	$[M]_D$ in benzene.	$[M]_D$ in alcohol.
Bornylamine	—	—	+ 87·3	+ 70·7
Methylbornylamine	+ 96·8	+ 161·6	160·1	135·3
Ethylbornylamine	93·0	168·3	163·4	136·4
n-Propylbornylamine	89·0	173·5	169·8	140·4
Butylbornylamine	81·7	170·7	167·8	135·4

Reference may be made to the work of Frankland and others.[1]

§ IV. *THE EFFECT OF THE LINKAGE OF THE CARBON ATOMS.*

1. Change from Single to Double Bond, and Double to Triple.—Walden[2] has studied this question by means of the active amyl esters of a series of saturated and unsaturated acids. He finds that unsaturation produces an increase in the rotatory power, but that the triple bond has less effect than the double one. As an example, the amyl esters of three acids may be quoted.

		$(\alpha)_D$	$(M)_D$
Hydrocinnamic ester	$C_6H_5 . CH_2—CH_2—COOC_5H_{11}$	$+ 2·26°$	$+ 4·68°$
Cinnamic ester	$C_6H_5—CH = CH—COOC_5H_{11}$	$+ 7·51°$	$+ 16·36°$
Phenylpropiolic ester	$C_6H_5—C \equiv C—COOC_5H_{11}$	$+ 5·58°$	$+ 12·05°$

The influence of the unsaturated bond upon the rotation becomes less the further away it is from the asymmetric carbon

[1] Carnelutti and Nasini, *Ber.*, **13**, 2208 (1880); Frankland and MacGregor, *Trans.*, **63**, 511, 1410 (1893); **65**, 750 (1894); Frankland and Wharton, *Trans.*, **69**, 1309 (1896); Frankland and Price, *Trans.*, **71**, 253 (1897); Guye and Chavanne, *Compt. rend.*, **116**, 1454 (1893); **119**, 906 (1894); **120**, 452 (1895); Anschütz and Reitter, *Zeit. physikal. Chem.*, **16**, 493 (1895); Tschugaeff, *Zeit. physikal. Chem.*, **17**, 245 (1895); *Ber.*, **31**, 360, 1775, 2451 (1898); *J. Russ. Phys. Chem. Soc.*, **34**, 606 (1902); MacCrae, *Trans.*, **81**, 1223 (1902); Wassmer and Guye, *J. Chim. Phys.*, **1**, 287 (1903); Minguin and Bollemont, *Compt. rend.*, **134**, 608 (1902); **136**, 238 (1903).

[2] Walden, *Zeit. physikal. Chem.*, **20**, 569 (1896).

atom. For example, in the following cases the phenyl group contains the unsaturated part of the molecule :—

Dibenzoyl-tartaric acid	$[\alpha]_D = 116–122^\circ$
Diphenacetyl-tartaric acid	$[\alpha]_D = 58^\circ$
Diphenpropionyl-tartaric acid	$[\alpha]_D = 38^\circ$

Zelinsky [1] has studied the same point in the alicyclic series, and finds that there also the ethylene bond tends to increase the rotatory power. The work of Rupe [2] and of Haller [3] on the camphor series may also be consulted.

2. Change from an Open-chain to a Cyclic Compound.—Ring-formation has an influence upon the rotation of a compound similar to that produced by unsaturation; in general, it raises the rotatory power.[4] This is shown in the relations of anhydrides and lactones to their parent acids :—

Diacetyl-tartaric acid	$[\alpha]_D = 59{\cdot}7^\circ$
Diacetyl-tartaric anhydride	$[\alpha]_D = 62{\cdot}0^\circ$
Xylonic acid	$[\alpha]_D = -7^\circ$
Xylonic lactone	$[\alpha]_D = +21^\circ$

As both ring-formation and unsaturation necessitate the loss of certain atoms from an open-chain compound, there may be some connection between the two phenomena; the more so since, as will be seen later, ring-compounds are in a state of unsaturation analogous in many ways to that found in the case of the double bond. An exception was noticed by Aschan,[5] who observed that camphoric anhydride had a very much lower rotation than camphoric acid. Here the ring-formation seems to depress the rotatory power.

3. Several Asymmetric Atoms in One Molecule.—In the

[1] Zelinsky, *Ber.*, **35**, 2494, 2682 (1902).
[2] Rupe, *Annalen*, **327**, 157 (1903).
[3] Haller, *Compt. rend.*, **136**, 1222; Haller and Desfontaines, *ibid.*, 1613 (1903).
[4] Haller and Desfontaines, *Compt. rend.*, **136**, 1613 (1903); **140**, 1205 (1905).
[5] Aschan, *Ber.*, **27**, 2011 (1894).

second edition of his book, *Die Lagerung der Atome in Raume*,[1] van't Hoff made the assumption that compounds containing several asymmetric groups have a rotatory power equal to the algebraic sum of the group rotations. Researches by Guye [2] and Walden [3] have established the truth of this idea. The method employed was as follows: Isomeric liquid amyl esters were made in three ways—(*a*) from an active acid and an inactive alcohol, (*b*) from an inactive acid and an active alcohol, and (*c*) from an active acid and an active alcohol. It was found that substances synthesized by method (*c*) had rotations equal to the sum of the rotations of the two isomeric bodies formed by methods (*a*) and (*b*). A variation of the same method was also used. Di- lævo-amyl ether :—

$$\begin{array}{lcl} CH_3\diagdown & & \diagup CH_3 \\ & CH—CH_2—O—CH_2—CH & \\ C_2H_5\diagup & & \diagdown C_2H_5 \end{array}$$

was examined, and its rotation determined. Lævo-amyl-bromide was then allowed to react with racemic sodium amylate, and the rotation of the mixture thus produced was found to be half as great as that of the ether with two active amyl radicals.

Rosanoff [4] disputes the correctness of van't Hoff's assumption, and states that he has found errors in the experimental work of Guye and Walden. He puts forward the proposition that the optical rotatory power of any asymmetric carbon atom depends on the composition, constitution, and configuration of each of the four groups to which it is attached. The work of Patterson and Taylor [5] on menthyl acetyl tartrates should be consulted.

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[1] P. 120.

[2] Guye, *Compt. rend.*, **119**, 740, 953 (1894); **120**, 632 (1895); **121**, 827 (1895); **122**, 932 (1896); Guye and Gautier, *Bull. Soc. chim.*, [3]; **11**, 1170 (1894); **13**, 457 (1895).

[3] Walden, *Zeit. physikal. Chem.*, **15**, 638 (1894); **17**, 705 (1895).

[4] Rosanoff, *J. Amer. Chem. Soc.*, **28**, 525 (1906). Compare Patterson and Kaye, *Trans.*, **89**, 1884 (1906).

[5] Patterson and Taylor, *Trans.*, **87**, 33 (1905).

§ V. THE HYPOTHESES OF GUYE AND CRUM BROWN.

Almost simultaneously, Crum Brown [1] and Guye [2] published papers embodying identical ideas, though they approached the problem from slightly different standpoints. In Crum Brown's view, the rotation of any compound depends upon four constants, one for each group attached to the asymmetric carbon atom; the actual rotation being proportional to the differences between the constants. In this form, the hypothesis does not meet the known facts.

Guye's statement of the case is somewhat different. He assumes that the carbon atom has the form of a regular tetrahedron, and that the radicals attached to it are also tetrahedrally grouped, though not necessarily regularly. He then calculates what he calls the "product of asymmetry," by multiplying together the lengths of the six perpendiculars drawn from the centre of gravity of the whole asymmetric system to the six planes of symmetry of the tetrahedral carbon atom. Three cases may then be foreseen. In the first, the groups attached to the asymmetric carbon atom are situated at the corners of a regular tetrahedron; in the second, they are still placed on the lines joining the centre of the carbon atom with its corners, but their distances from the centre are not equal; while in the third case they are neither on these lines, nor are they equidistant from the centre. The first case is the only one which can be dealt with, and Guye assumes that the variations from it in the second and third cases are of little importance. If we suppose that the masses of the four groups attached to the asymmetric carbon atom are represented by a, b, c, and d; and that their distances from the centre of the carbon tetrahedron are all equal to l; then the value of P will be found from the following equation:—

$$P = \frac{(a-b)\ (a-c)\ (a-d)\ (b-c)\ (b-d)\ (c-d)}{(a+b+c+d)^6} \cdot (l \sin 54^\circ 44')$$

[1] Crum Brown, *Proc. Roy. Soc. Edin.*, **17**, 181 (1890).
[2] Guye, *Compt. rend.*, **110**, 714 (1890); **116**, 1378, 1451 (1893).

This equation satisfies the two necessary conditions—(1) that when any two or more of the masses a, b, c, and d become equal, P becomes zero, since the asymmetry is destroyed; and (2) that the product must be the same though with an opposite sign when any two of the values a, b, c, and d are transposed, as this corresponds to the conversion of a configuration into its mirror-image.

Two deductions can be made from the equation—

1. If the group with the greatest mass be altered in such a way that while changing its value it still remains the most massive of the four, then the rotation of the compound should change in value but remain of the same sign (*i.e.* either right or left rotating).

2. If we consider a right rotating compound such that $a > b > c > d$ and replace a by a', a group with gradually decreasing mass, we should find that when—

$a' > b$, there should be either a continuous decrease in the right rotation, or first, an increase to a maximum with a subsequent decrease;
$a' = b$, inactivity is produced;
$a' < b$, a change to left rotation, increasing to a maximum, and then decreasing;
$a' = c$, a second condition of inactivity is produced;
$a' < c$, right rotation appears, increasing to a maximum and then decreasing;
$a' = d$, a third condition of inactivity is produced;
$a' < d$, there is increasing left rotation.

Investigations by Walden[1] have pointed to many facts which cannot be reconciled with the hypothesis. For instance, it has been found that in some compounds which have two or three groups of equal weight (*e.g.* methyl-acetyl-mandelic methyl ester):—

$$\begin{array}{c} CH_3 \\ | \\ C_6H_5—C—COOCH_3 \\ | \\ CH_3CO.O \end{array}$$

[1] Walden, *Zeit. physikal. Chem.*, **15**, 638 (1894); **17**, 245, 705 (1895).

or phenyl-brom-acetic ethyl ester, where the molecular weight of the phenyl group, 77, differs but slightly from the atomic weight of the bromine atom, 80:—

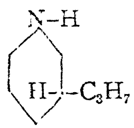
$$\begin{array}{c} \mathrm{Br} \\ | \\ C_6H_5\text{—}\mathrm{C}\text{—}COOC_2H_5 \\ | \\ \mathrm{H} \end{array}$$

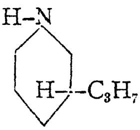
inactivity should be found if the hypothesis were true; whereas the compounds are really active. Again, a change in the order of two group-weights, which, according to Guye, should be accompanied by a change in the direction of rotation, does not produce this effect. In homologous series the changes in rotatory power do not agree, in the majority of cases, with the changes in the product of asymmetry.

Guye[1] admits that his hypothesis requires modification, as many other influences must come into play of which his statement of the problem takes no account; but, nevertheless, it would seem that a great, though not a preponderating, influence is brought to bear by the masses of the four groups producing asymmetry. The question seems to be so complicated, however, that a complete solution will probably never be found.

[1] Guye, *Bull. Soc. chim.*, [3] **15**, 195 (1896).

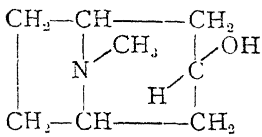
from coniine in optical rotation, as well as in other properties. The explanation put forward for this was that the hydrogen atom attached to the nitrogen lay on opposite sides of the ring in the two isomers.



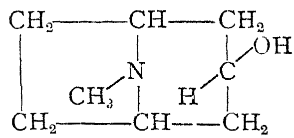


Ladenburg also found a similar instance in stilbazoline and isostilbazoline. The accuracy of Ladenburg's work, however, has been called in question by Wolffenstein.[1]

The isomerism of tropine and ψ-tropine has also been referred to a similar difference in spacial relations, the two formulæ proposed being :—



and



but another explanation is given in Appendix A.

§ II. *PENTAVALENT NITROGEN.*

1. Compounds of the Type : abcdNX.—Before compounds of this class were actually isolated in active forms, several unsuccessful attempts were made by various investigators. Le Bel[2] allowed ordinary mould to act upon dilute solutions of methyl-ethyl-propyl-isobutyl-ammonium chloride, and methyl-ethyl-propylamine hydrochloride; and in the former case observed a very slight activity. The active chloride was isolated and analysed by means of the gold and platinum double salts. The acetate prepared from the chloride and silver acetate was also active. On the other hand, when the mercury- or

[1] Wolffenstein, *Ber.*, **27**, 2615 (1894).
[2] Le Bel, *Compt. rend.*, **112**, 724 (1891).

platinum-chloride salt was treated with sulphuretted hydrogen, it became practically inactive: the same change being noticed with the gold salt, in which case, however, the effect was not so marked. This effect is probably produced by the libeiated hydrochloric acid.

Marckwald and Droste-Huelshoff[1] repeated Le Bel's work, but failed to confirm it. Le Bel[2] then published furthei information on the subject. He found that the methyl-ethyl-isopropyl-ammonium salts exist in two forms, whose properties differ somewhat as follows: The α-salts are more soluble than the β-salts. The α-chloride is more easily attacked by ferments than the β-chloride. After resolution by means of ferments, the α-chloride produces the left-rotating active form; while the β-chloride yields the right-rotating form. If hydrochloric acid be allowed to act upon a mixture of the active α- and β-chlorides, the α-chloride is racemised, while the β-chloride retains its dextro-rotation. Further, differences were observed in the amounts of the two inactive salts formed, according to the order in which groups were first introduced into the molecule. Le Bel also stated that he had succeeded in the cases of solutions of isobutyl-propyl-amyl- and ethyl-propyl-amyl-ammonium salts.

Pope and Peachey,[3] by using *d*-camphorsulphonic acid, were able to resolve α-phenyl-benzyl-allyl-methyl-ammonium iodide. The salts were crystallized from non-hydroxylic solvents, ethyl acetate or acetone. Pope and Harvey investigated the compounds so produced.[4] The *d*-camphorsulphonate of the *d*-base had a molecular rotatory power of $[M]_D = 218°$, in dilute aqueous solution, the corresponding *l-l* salt having $[M]_D = -211°$; while the iodides had a molecular rotation of approximately $\pm 200°$ in chloroform. The rotation of the iodides disappears completely when their chloroform solution is warmed or allowed to stand for a few days: the resulting

[1] Marckwald and Drostehuelshoff, *Ber.*, **32**, 560, 3508 (1899).
[2] Le Bel, *Compt. rend.*, **129**, 548 (1904).
[3] Pope and Peachey, *Trans.*, **75**, 1127 (1899).
[4] Pope and Harvey, *Trans.*, **79**, 828 (1901).

compound is α-benzyl-phenyl-allyl-methyl-ammonium iodide, and not the isomeric β-compound. The activity of the salts is not lost by recrystallization from alcohol. It was also found that the optically active ammonium salts differ from the optically active carbon compounds in that the former yield in solution active ions whose free affinities are attached to the asymmetric nitrogen; yet no racemisation ensues.

Jones,[1] in a similar manner, resolved phenyl-benzyl-ethyl-methyl-ammonium iodide. The *d-d* and *l-l* camphorsulphonates had $[M]_D = \pm 71°$.

Thomas and Jones[2] have studied the influence of constitution upon the rotation of nitrogen compounds, using compounds of the types *d*-phenyl-benzyl-methyl-ethyl-ammonium-*d*-camphorsulphonate and *d*-phenyl-methyl-ethyl-allyl-ammonium-*d*-bromo-camphorsulphonate. It was found that in general, when higher homologues of these substances were prepared, their rotations differed from those of the lower members of the series. A maximum was reached in the case of the normal or isopropyl derivatives.

Wedekind and Fröhlich[3] observed that when *l*-methyl-isobutyl-phenyl-benzyl-ammonium iodide, $(CH_3)(C_4H_9)(C_6H_5)(C_6H_5CH_2)N.I$, was allowed to stand in chloroform solution, autoracemisation took place. Wedekind[4] has measured the velocity of this racemisation in certain other cases.

2. Cyclic Ammonium Compounds.—So far no substances of this type seem to have been resolved.

3. Compounds of the Type a_2bcNX.—Le Bel,[5] Jones,[6] Kipping and Barrowcliff,[7] have all tried to resolve substances of this class, but without success.

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[1] Jones, *Trans.*, **83**, 1418 (1903); **85**, 223 (1904).
[2] Thomas and Jones, *Trans.*, **89**, 280 (1906).
[3] Wedekind and Frohlich, *Ber.*, **38**, 3933 (1905).
[4] Wedekind, *Zeit. Electrochem.*, **12**, 330 (1906).
[5] Le Bel, *Compt. rend.*, **112**, 724 (1891).
[6] Jones, *Trans.*, **83**, 1406 (1903).
[7] Kipping and Barrowcliff, *Trans.*, **83**, 1141 (1903).

§ III. *THEORETICAL VIEWS ON THE CONFIGURATION OF NITROGEN COMPOUNDS.*

Having thus surveyed the cases in which isomerism is known to occur among the nitrogen compounds, we must now deal with the theories put forward at various times as to the configuration of those molecules which owe their optical activity to the presence of an asymmetric nitrogen atom.

It is impossible to arrange five points symmetrically upon the surface of a sphere except at equal distances round a great circle; so in the case of pentavalent nitrogen an exception to the usual theory must be made, and some distinction must be drawn between the valencies. In one attempted solution of the problem the assumption is made that the valencies of a pentavalent nitrogen atom are directed toward the corners of a double pyramid at whose centre the atom itself lies. Suggestions of this kind have been put forward at various times by Willgerodt,[1] Burch and Marsh,[2] Behrend,[3] Béhal,[4] and van't Hoff.[5] It will be sufficient to give an account of the last of these.

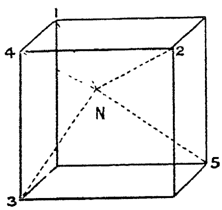
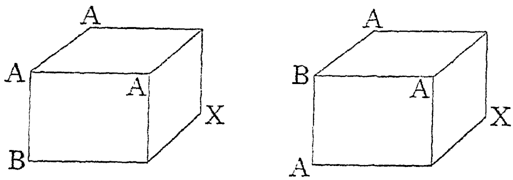


FIG. 23.

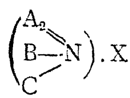
Van't Hoff supposes that the nitrogen atom occupies the centre of a cube, toward five corners of which the five valencies of the nitrogen atom are directed. In the above figure, where

[1] Willgerodt, *J. pr. Chem.*, [2] **37**, 450 (1888); **41**, 291 (1890).
[2] Burch and Marsh, *Trans.*, **55**, 656 (1889).
[3] Behrend, *Ber.*, **23**, 454 (1890).
[4] Béhal, *Conférences de la chimie*, IV. 60–63 (1896).
[5] Van't Hoff, *Ansichten uber die organische Chemie*, p. 79.

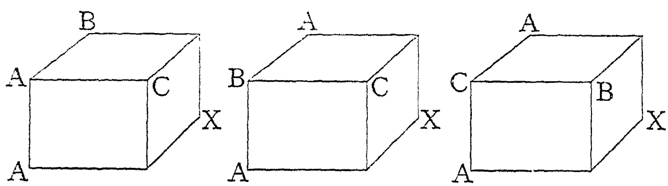
the valencies are represented by dotted lines, it is evident that those valencies directed to 1, 2, and 3 are of equal value; while those directed to 4 and 5 are different from each other and from all the rest. This difference is made in view of the fact that, though ammonia will unite with hydrochloric acid, it will not combine with two hydrogen atoms or two chlorine atoms; and it is postulated that one of the two valencies 4 and 5 is utilised in holding the negative radical of ammonium salts. If we suppose that this special valency is the one directed toward 5, we shall find that for the compound $(A_3 \equiv N.B).X$ there are two possible configurations which may be represented thus :—



If a new radical be introduced into the ammonium salt instead of one of the A radicals, the salt will become :—

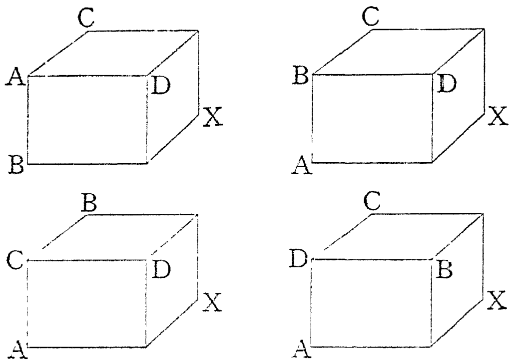


and there would be four possible configurations, three of which are shown below :—



The first of these three isomers is not superposable upon its mirror-image, so that compounds of this type ought to give rise to optically active forms. Up to the present, no such

isomers have been shown to exist. If another of the A groups be replaced by a new radical, four different configurations can be obtained, each having a mirror-image different from itself. As has just been shown, however, compounds of the type *abcd*NX have so far been known to give rise to only a single pair of isomers.



The van't Hoff hypothesis cannot be brought into agreement with the facts known at present.

There are three other theories which must be described. The first is due to Bischoff,[1] who suggested that ammonium chloride could be represented by the pyramidal figure :—

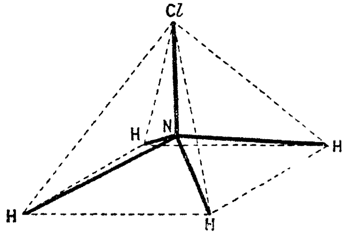


FIG. 24.

Now, in the case of a substituted ammonium salt, it is obvious

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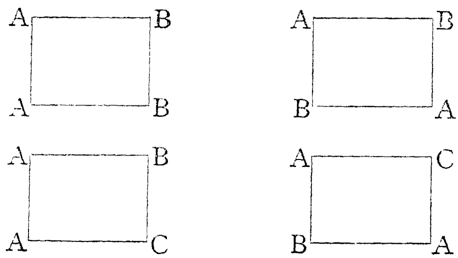
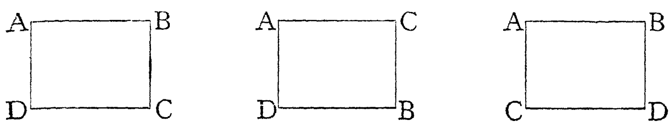
[1] Bischoff, *Ber.*, **23**, 1970 (1890) ; see also Reychler, *Bull. Soc. chim.*, [3] **27**, 974 (1902).

that, in calculating the isomerism possibilities, only the radicals arranged about the base of the pyramid need be considered, since in all cases the acid radical remains fixed to the apex of the pyramid, no matter how the other groups are changed. The question therefore is reduced to one dealing with the relations of four radicals lying in one plane. There will be no isomerism in the case of the salt $(N.A_3B)X$; compounds of the types $(N.A_2B_2)X$ and $(N.A_2BC)X$ will exist in two configurations, some of which can be superposed upon their mirror-images. The figures below show the arrangement of the radicals around the base of the pyramid in these cases:—

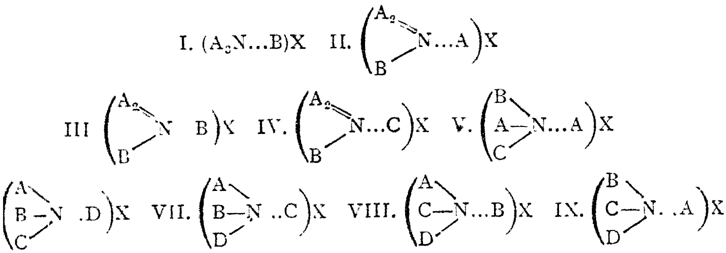


No such isomers are known. In the case of those compounds where the nitrogen atom is attached to five different radicals, there are three isomers possible, each of which could exist in active forms:—



Werner has applied his theory of "main-" and "subsidiary-valencies" to the question. According to his view, the compound of HX with N*abc* is formed by the attraction of the nitrogen atom for the hydrogen. After the union of the two has taken place, there remains over in the group N*abc*H sufficient affinity to attract and hold the halogen atom X. Since X is held by the whole group N*abc*H, and not by the

nitrogen atom alone, it plays no part in the stereochemical properties of the compound from the point of view of valency; but it must be considered as lying in space near one of the radicals united with the nitrogen atom. Taking the same compounds as were dealt with in the last case, we find the following possibilities:—



We have thus the same number of isomers as were derived from the van't Hoff model. If, however, we neglect the position of X, and regard it as attached to the group *abcd*N as a whole, we need then consider only the space relations of the group N*abcd*, the case is parallel to that of the asymmetric carbon atom. The results can then be brought into line with the experimental evidence.

The last space formula which need be mentioned is due to H. O. Jones.[1] It appears to be the only one which agrees with the known facts. Jones disputes the correctness of the assumption made in the case of the van't Hoff formula, as regards the difference between the two "abnormal" valencies, and points out that if one of the new valencies were predestined to be the one attached to the alkyl group, or the acidic radical, only one of the two optical isomers would be formed, whereas in practice the *d*- and *l*- compounds are formed in equal quantities. It has already been shown that there is good ground for believing that in a compound N*abc*, the three groups *a*, *b*, and *c* lie in one plane with the nitrogen atom itself. Now, when a trivalent compound combines with two

[1] H. O. Jones, *Trans.*, **83**, 1403 (1903); **87**, 1721 (1905).

new radicals, so that the nitrogen atom becomes pentavalent, this equilibrium is disturbed and new equilibrium positions must be found, which will be determined by the mutual attractions of the atoms involved. There will, therefore, be a definite spacial arrangement of the atoms, and the fifth group, being electronegative while the other four are electropositive, will always bear approximately the same relation to each of these four groups. A change of valency position similar to that which occurs when sulphur and selenium change their valency from four to six [1] is therefore assumed to take place. The following scheme gives a representation of the processes involved:—

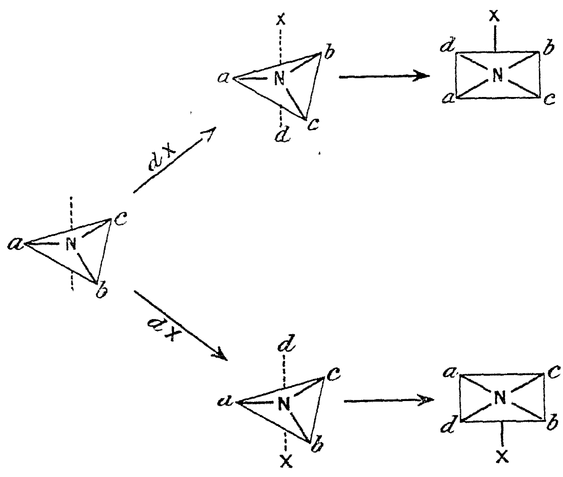


FIG. 25.

The two compounds thus produced are mirror-images of one another. It should be noticed that the *order* of the three groups already present in the trivalent nitrogen compound is not altered by the rearrangement. The group *d* is supposed to be capable of interposing itself between two of the groups, in the way which leads to the most stable configuration being

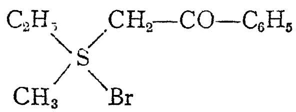
[1] Pope and Neville, *Trans.*, **81**, 1560 (1902).

produced. From this it can be seen that in the formation of the compound N*abcd*X from N*abc* and *d*X, from N*abd* and *c*X, or in either of the other two possible ways, the end-product will always be the same. This theory explains all the known facts, and is probably near the truth.

Sulphur.

Several fruitless attempts to isolate active sulphur compounds were made by various investigators, among whom were Aschan,[1] Vanzetti,[2] Strömholm,[3] and Pope and Peachey.[4]

Smiles,[5] from ω-bromacetophenone and methyl-ethyl-sulphide, synthesised the glassy sulphine bromide :—



from which the bromocamphorsulphonate was made. Two salts were isolated :—

(1) Colourless needles	M.P. 194–195°	$[\alpha]_D = +49{\cdot}7^\circ$
(2) Fine needles	M.P. 183–184°	$[\alpha]_D = -57{\cdot}2^\circ$

from which crystalline picrates were formed in golden needles—

l-picrate	M.P. 125°	$[\alpha]_D = -9{\cdot}2^\circ$
d-picrate	M.P. 123·4°	$[\alpha]_D = +8{\cdot}1^\circ$

Pope and Neville[6] found somewhat higher values for the same compound.

Pope and Peachey[7] succeeded in producing active salts of methyl-ethyl-thetine by means of camphorsulphonic acid and bromocamphorsulphonic acid.

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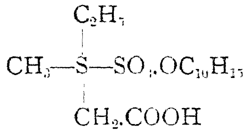
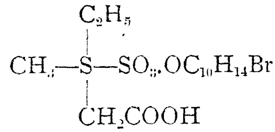
[1] Aschan, *Ber.*, **32**, 993 (1899).
[2] Vanzetti, *Gazzetta*, **30**, I., 175 (1900).
[3] Stromholm, *Ber.*, **33**, 823 (1900).
[4] Pope and Peachey, *Proc*, **16**, 12 (1900).
[5] Smiles, *Trans.*, **77**, 1174 (1900).
[6] Pope and Neville, *Trans.*, **81**, 1097 (1902).
[7] Pope and Peachey, *Trans.*, **77**, 1072 (1900).

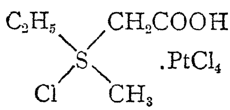

(I.)


(II.)

The first salt, M.P. 115–117°, after being fractionally crystallized forty or fifty times from a mixture of ether and alcohol, goes over into a second modification, melting at 118–120°. The rotation values of the two salts are:—

	(1)	(2)
$[\alpha]_D$	$+18{\cdot}6°$	$+62{\cdot}7°$
$[M]_D$	$+68{\cdot}0°$	$+290{\cdot}5°$

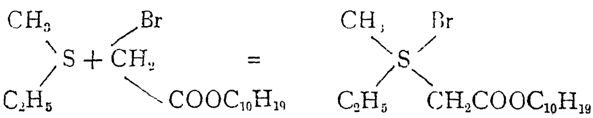
From both salts, by treating with hydrochloric acid and precipitation with platinum chloride, the following double salt (M.P. 177–180°) can be obtained:—



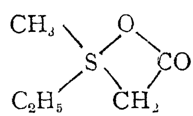
$[\alpha]_D = +\ 4{\cdot}5°$
$[M]_D = +30{\cdot}2°$

The activity in the last case can originate only in the sulphur atom.

Smiles[1] prepared methyl-ethyl-thetine-bromide-*l*-menthyl ester from *l*-menthyl-bromoacetate and methyl-ethyl-sulphide.



which, when hydrolysed with moist silver oxide or hydrochloric acid, gives:—

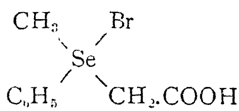

(Inactive)

[1] Smiles, *Trans.*, **87**, 450 (1905).

He found that (*a*) the product yields an inactive methyl-ethyl-thetine on saponification with silver oxide, or with cold concentrated hydrochloric acid; (*b*) that the molecular rotatory power of the product lies nearly half-way between those of the dimethyl and diethyl derivatives; (*c*) that the platinichloride of *dl*-methyl-ethyl-thetine-*l*-menthyl-ester bromide, when prepared from *l*-menthol and the acid bromide of *dl*-methyl-ethyl-thetine has the same rotatory power as the platinichloride made from the product of asymmetric synthesis. Hence it is concluded that the two isomeric *d*- and *l*- methyl-ethyl-thetine-*l*-menthyl-ester bromides are produced in equal amount from the interaction of methyl-ethyl-sulphide and *l*-menthyl bromoacetate.

SELENIUM.

Pope and Neville [1] have described the isolation of an active selenium compound. They allowed methyl-phenyl-selenide to act upon bromoacetic acid, producing methyl-phenyl-selenetine bromide :—



When this is treated with the silver salt of *d*-bromocamphor-sulphonic acid, it yields a mixture of :—

(*a*) *d*-methyl-phenyl-selenetine-*d*-bromocamphorsulphonate (needles, M.P. 168°; $[\alpha]_D = 61 \cdot 26°$ in water).

(*b*) *l*-methyl-phenyl-selenetine-*d*-bromocamphorsulphonate (small white plates, M.P. 151°; $[\alpha]_D = 38 \cdot 81°$, in aqueous solution).

The second salt is much more soluble in alcohol than the first. The molecular rotations of the two salts are :—

$$(a)\ [M]_D = +330 \cdot 8°$$
$$(b)\ [M]_D = +209 \cdot 6°$$

[1] Pope and Neville, *Trans.*, **81**, 1552 (1902).

th isomeric *d*-bromocamphorsulphonates give the same in-ive double salt with mercuric iodide: racemisation therefore curs.

TIN.

In 1900, Pope and Peachey[1] synthesised a compound ich contained one atom of tin directly united with four ferent groups. By the following series of reactions, they oduced methyl-ethyl-propyl-stannic iodide:—

$$n(CH_3)_3I + Zn(C_2H_5)_2 = 2Sn(CH_3)_3C_2H_5 + ZnI_2$$
$$(CH_3)_3C_2H_5 + I_2 = Sn(CH_3)_2(C_2H_5)I + CH_3I$$
$$n(CH_3)_2(C_2H_5)I + Zn(C_3H_7)_2 = 2Sn(CH_3)_2(C_2H_5)(C_3H_7) + ZnI$$
$$(CH_3)_2(C_2H_5)(C_3H_7) + I_2 = Sn(CH_3)(C_2H_5)(C_3H_7)I + CH_3I$$

e end-product, externally compensated methyl-ethyl-propyl-stannic iodide, is a yellow oil almost insoluble in ter. Its boiling-point is 270°. When it is treated with an uimolecular quantity of silver *d*-camphorsulphonate, it yields salt which crystallizes in shining plates of M.P. 125–126°. e salt's $[M]_D$ is $+9{\cdot}5°$, so that the molecular rotatory wer of the radical $-Sn(CH_3)(C_2H_5)(C_3H_7)$ is about $+45°$. is was, therefore, the right-rotating component. When e mother-liquor was evaporated, however, *the same* salt was und; and in no way could the *l*-variety be produced. The bromocamphorsulphonate was also made, and found to have rotation of $+48°$ for the monovalent radical shown above. e *d*-methyl-ethyl-*n*-propyl-stannic iodide was also prepared, d found to be a yellow oil with a molecular rotation of $+23°$. eculiar racemisation phenomena were observed in the case this substance.

HEORETICAL VIEWS ON THE CONFIGURATION OF SULPHUR, SELENIUM, AND TIN COMPOUNDS.

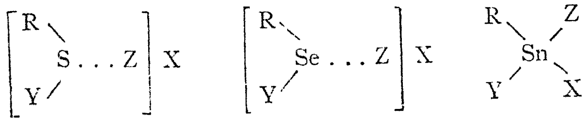
Pope and Neville[2] have adopted the idea that in tive compounds of a quadrivalent element the radicals are

[1] Pope and Peachey, *Proc.*, **16**, 42; 116 (1900).

[2] Pope and Neville, *Trans.*, **81**, 1552 (1902).

tetrahedrally arranged around the central atom, just as in the case of carbon; and they were able to explain certain racemisation phenomena by the assumption that an intermediate compound was formed by the conversion of the quadrivalent element into a hexavalent state.

Werner[1] dwells upon the fact that, though the tin derivatives certainly resemble the carbon compounds, the sulphur and selenium derivatives show a greater likeness to the ammonium type. With this in view, he prefers to write the formulæ of the two series differently:—



In the last case the system is the same as in the carbon compounds: in the other two instances the tetrahedral arrangement is supposed to be due to the relations between the atoms within the square bracket:—

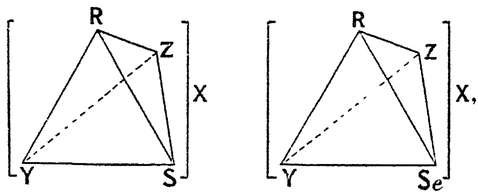
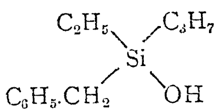


FIG. 26.

SILICON.

Kipping[2] has succeeded in preparing *dl*-benzyl-ethyl-propyl-silicol:—



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[1] Werner, *Lehrbuch der Stereochemie*, p. 316.
[2] Kipping, *Trans.*, **91**, 209 (1907).

and resolving its sulphonic derivatives into optically active components.

Iodine.

Kipping and Peters[1] endeavoured to resolve iodonium compounds of the type I*abc*. The results were negative.

Arsenic.

Michaelis's[2] attempts to resolve arsenic compounds of the type As*abcd*X were also fruitless.

Phosphorus.

R. M. Caven[3] was able to show that in a molecule of phosphoryl chloride, the three chlorine atoms are identical in properties :—

$$\begin{matrix} Cl\diagdown & & \\ Cl\text{—} & P = O \\ Cl\diagup & & \end{matrix}$$

It is therefore probable that they lie in one plane. If this be so, then the molecule :—

$$\begin{matrix} R_1\diagdown & & \\ R_2\text{—} & P = O \\ R_3\diagup & & \end{matrix}$$

will be asymmetric, whether the phosphorus atom lies in the same plane as the radicals R_1, R_2, R_3 or not. Attempts to produce active salts of this type, however, were not successful.

Owing, possibly, to the injurious action of phosphonium compounds upon ferments, Michaelis[4] was unable to resolve compounds of the type P*abcd*X.

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[1] Kipping and Peters, *Proc.*, **16**, 62 (1900); Peters, *Trans.*, **81**, 1350 (1902).

[2] Michaelis, *Annalen*, **321**, 159 (1902).

[3] Caven, *Trans.*, **81**, 1362 (1902).

[4] Michaelis, *Annalen*, **315**, 58 (1901).

CHAPTER IX.

ROTATION.

§ I. *THE VARIATION OF THE SPECIFIC ROTATION OF DISSOLVED SUBSTANCES.*

1. The Effect of varying the Concentration.—In 1838 Biot,[1] in studying the behaviour of aqueous solutions of tartaric acid, found that as the solution was diluted the specific rotation increased. This is not the case with all substances, however, for when solutions of camphor and coniine in alcohol are diluted, the specific rotation diminishes. The phenomenon must be due to some action of the inactive solvent upon the active substance.

This would not be of much importance were it possible to take the rotation of all substances in the liquid state; but as that is impossible in some cases, means have to be devised for finding the true specific rotation of a substance in solution.

If we consider the case of a substance dissolved in a pure homogeneous liquid, we may represent the effects of varying concentrations upon the specific rotation in the following manner. Taking two rectangular axes, measure along the one lengths corresponding to the percentages of inactive solvent in the mixture (q), while the length of the ordinate corresponding to each abscissa is made proportional to the value of the specific rotation for that degree of concentration. If the line joining the ends of the ordinates be straight, it will be represented by the equation :—

$$[\alpha] = A + Bq \quad . \quad . \quad . \quad . \quad . \quad . \quad (D)$$

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[1] Biot, *Mem. de l'Acad.*, **15**, 93 (1838) ; *Ann. Chim. Phys.*, [3] **10**, 385 (1843).

where A and B are constants, which can be calculated from experiments. If it be not straight, the equation will take some other form; *e.g.*—

$$[\alpha] = A + Bq + Cq^2 ; \text{ or } [\alpha] = A + \frac{Bq}{C+q} \quad . \quad \text{(E)}$$

In these formulæ A represents the true specific rotation of the pure substance, while the values of B in formula (D) and of B and C in (E) depend on the amount of variation from this produced by the addition of 1 per cent. of inactive solvent. This may be easily proved,* as follows:—

Put $q = 0$ in (D) or (E).

$$\text{Then } [\alpha] = A.$$

Similarly, put $q = 1$. Then B or B and C depend on the change in rotation produced by the addition of 1 per cent. of inactive solvent.

Other modifications of these formulæ are sometimes used, but for a discussion of them the reader is referred to Landolt's book.

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* The following alternative proof is given by Landolt:—

From equations (C), on p. 15, and (D) we have:—

$$\frac{100 \,.\, \alpha}{l \,.\, p \,.\, d} = [\alpha] = A + Bq$$

Now, $p = 100 - q$.

$$\therefore \frac{100 \,.\, \alpha}{l \,.\, d(100 - q)} = A + Bq$$

$$\text{and } \alpha = l \,.\, d \left\{ A + \left(B - \frac{A}{100}\right)q - \frac{B}{100}q^2 \right\}$$

If q be put equal to 100, then α becomes zero, there being no rotation in a solution of infinite dilution. If q be put equal to zero, then α becomes equal to $l \,.\, d \,.\, A$, that is, the angle of rotation shown by a column of pure substance 1 decimetre long with a specific gravity d. (See Formula A, on p. 15.)

$$\text{Hence } \frac{\alpha}{l \,.\, d} = A$$

$$\text{but } \frac{\alpha}{l \,.\, d} = [\alpha]$$

$$\therefore A = [\alpha]$$

which is the specific rotation of the substance without any solvent.

From the above, it will be seen that in order to find the true specific rotation of a solid active substance, three observations at different concentrations must first be made, from which it will be possible to determine whether the relation between the specific rotation and the concentration can be graphically represented by a straight line or not. If it can be so represented, extrapolation can at once be resorted to, and the true specific rotation obtained; but if the line be a curve, many observations will be necessary to define it exactly, and only after these have been made can extrapolation be safely employed.

2. The Effect of varying the Solvent.—The nature of the solvent chosen appears to have a considerable effect upon the specific rotation. For instance, *d*-tartaric acid, which in aqueous solutions is dextro-rotatory, becomes lævo-rotatory when it is dissolved in a mixture of ether and acetone. In those substances where the effect is not quite so marked as this, the specific rotation is increased by some solvents and decreased by others.

For example, normal propyl diacetyl-tartrate shows the following specific rotations in different solvents.[1] The pure ester alone has a specific rotation $[\alpha]_D = 13{\cdot}3^\circ$.

Solvent.	$[\alpha]_D$
Carbon disulphide	$36{\cdot}7^\circ$
Acetone	$10{\cdot}4^\circ$
Ethyl alcohol	$9{\cdot}6^\circ$
Ethylidene chloride	$6{\cdot}4^\circ$
Carbon tetrachloride	$3{\cdot}8^\circ$
Benzene	$1{\cdot}2^\circ$

The chief workers in this field have been Frankland and Pickard,[2] Patterson,[3] and Purdie and Barbour.[4]

[1] Freundler, *Compt. rend.*, **117**, 556 (1893); *Ann. Chim. Phys.*, [7] **4**, 244 (1895).

[2] Frankland and Pickard, *Trans.*, **69**, 123 (1896).

[3] Patterson, *Trans.*, **79**, 167, 477 (1901); **81**, 1097, 1134 (1902); **85**, 1116, 1153 (1904); Patterson and Taylor, *Trans.*, **85**, 122 (1905).

[4] Purdie and Barbour, *Trans.*, **79**, 937 (1901).

3. The Effect of varying the Temperature.—An increase in temperature brings about a change in specific rotation, but this change differs for each substance; the rotations of some bodies are increased, while those of others are diminished.[1] No definite rule can be laid down in this case.

4. Some Causes of Changes in Specific Rotation.—(*a*) *Electrolytic Dissociation.*—The first experiments which threw any light upon this subject were made by Landolt,[2] in the course of an investigation of the metallic tartrates. He noticed that many neutral tartrates had the same molecular rotation, and that the metallic atoms appeared to exercise no great influence. Similar results were observed in the case of an active alkaloid dissolved in inactive acids. A further step was made when it was found that salts of malic acid or camphoric acid, which gave very different rotations in concentrated solutions, tended to give approximately equal rotations when the solutions were sufficiently diluted.[3] Free malic acid had a rotation different from that of its salts.

Hädrich[4] was the first to give a satisfactory explanation of these phenomena. Assuming that the salts of active acids or bases, when in sufficiently dilute solution, become dissociated into their ions, he pointed out that this was sufficient to explain the facts; and he formulated the case as follows: "The rotating power, in approximately completely dissociated solutions, not only of salts, but of electrolytes in general, is independent of the ion."

The apparent difference between malic acid and its salts was explained by the fact that the acid itself is not a good electrolyte. On the other hand, Rimbach's results[5] seem to

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[1] Guye and Amaral, *Compt. rend.*, **120**, 1345 (1895); Guye and Aston, *Compt. rend.*, **124**, 194 (1897); **125**, 819 (1897); Frankland and McGregor, *Trans.*, **65**, 760 (1894); **69**, 104 (1896); Frankland and Wharton, *Trans.*, **69**, 1309 (1896); Walden, *Ber.*, **36**, 781 (1903); Guye and Wassmer, *J. chim. phys.*, **1**, 257 (1903); Patterson, *Trans.*, **85**, 765 (1904); Grossmann and Potter, *Ber.*, **37**, 84, 1260 (1903).

[2] Landolt, *Ber.*, **6**, 1077 (1873).

[3] Schneider, *Annalen*, **207**, 257 (1881).

[4] Hadrich, *Zeit. physikal. Chem.*, **12**, 476 (1893).

[5] Rimbach, *Zeit. physikal. Chem.*, **28**, 251 (1899)

point to the fact that the rotation of electrolytes is independent of their degree of ionisation.

(*b*) *Molecular Aggregations in Solutions.*—When acetic acid is dissolved in ether, its molecular weight is normal, corresponding to $C_2H_4O_2$, but if it be dissolved in benzene, the result appears to be an aggregation of two molecules, giving a molecular weight of $(C_2H_4O_2)_2$. This might lead to the conclusion that, when anomalous rotations have been observed, they might be due to the presence in solution of some such aggregation. With a view to deciding this question, investigations were carried out by several observers,[1] with the result that in some cases there appears to be a connection between aggregation and abnormal rotation, while in others no such relation can be traced.

(*c*) *Complex Polymerised Molecules in the Solution (Crystal Molecules).*—A few compounds are known which possess the power of rotating the plane of polarization both when in the solid state and when in solution; and in their case it has been observed that their rotation in the solid state differs from that shown by their solution. This difference has been ascribed to the fact that while their rotations in the state of solution are due solely to the intramolecular arrangement of their atoms, their rotation in the crystalline state is further modified by the form in which they crystallize.

The same reasoning has been applied to the case of some abnormalities of rotation in the case of dissolved bodies. It is assumed that if, in a solution, a sufficient number of molecules form an aggregation, they may produce an effect upon the plane of polarization comparable to that caused by the form of the crystal in the case of solid strychnine sulphate.

Two examples may be described, in order to make the point clear. In concentrated solutions, malic acid shows dextro-rotation; but, on dilution, this decreases, passes through zero, and finally is changed to lævo-rotation.[2] A lowering

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[1] Freundler, *Ann. Chim. Phys.*, [7] **4**, 256 (1895); Pescetta, *Gazzetta*, **25**, II., 418 (1895); Walden, *Zeit. physikal. Chem.*, **17**, 705 (1895); Frankland and Pickard, *Trans.*, **69**, 123 (1896).

[2] Schneider, *Annalen.*, **207**, 257 (1881).

of the temperature produces somewhat similar results.[1] With *d*-tartaric acid, the effect is reversed, the rotation passing from left to right as the dilution is increased.[2]

These phenomena cannot be explained by electrolytic dissociation, because since malic and tartaric acids are not good electrolytes, this dissociation could only be expected in dilute solutions; nor can the cause be looked for in simple polymerization, for molecular weight determinations show that the molecular weight under the conditions of the experiment is normal; and lastly, it is not due to the formation of hydrates in the solution.[3] This point will be dealt with later.

The following explanation seems to be the most probable one. It is assumed that single molecules of malic acid are dextro-rotatory, but that in a concentrated solution they are capable of building up a structure of several molecules which has lævo-rotation. This was tested by determining whether *d*-tartaric acid in the solid state was also lævo-rotatory, which was found to be the case.[4] Later, Walden showed that similar relations held good for malic acid.[5]

This explanation makes clear also the reason why some bodies in certain solvents exhibit a variety of rotation different from that which they show when dissolved in other liquids, as some solvents favour the formation of such crystal molecules, while others have not this effect.

It should be clearly understood, however, that the question is still under discussion; and no definite conclusion has yet been drawn. The matter is discussed in detail in one of Walden's papers,[6] with which Patterson's criticism[7] must be compared.

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[1] Thomsen, *Ber.*, **15**, 441 (1882)

[2] Arndtsen, *Ann. Chim. Phys.*, [3] **54**, 403 (1858); *Ann. d. physik*, **105**, 312 (1858).

[3] Nasini and Gennari, *Zeit. physikal. Chem.*, **19**, 113 (1896).

[4] Biot, *Ann. Chim. Phys.*, [3] **28**, 351 (1850).

[5] Walden, *Ber.*, **32**, 2849 (1899).

[6] Walden, *Ber.*, **38**, 345 (1905).

[7] Patterson, *Ber.*, **38**, 4090 (1905).

(*d*) *Combinations of the Active Body with the Solvent.*—Attempts have been made to explain the change in specific rotation brought about by dilution on the assumption that hydrates of the active substance are formed which contain more water the more dilute the solution becomes. This has been proved to be improbable, as for all concentrations the ratio of hydrated to unhydrated molecules in most cases remains the same.[1] But though the general formation of hydrates must be considered as improbable, there is no doubt that in certain cases compounds are formed which have an effect upon the rotation of the substances which produce them. Reference may be made to the cases of nicotine,[2] malic acid,[3] rhamnose hydrate,[4] and the results found with propyl tartrate in benzene[5] and certain alkaloids in alcohol and benzene.[6]

(*e*) *Hydrolysis.*—No definite information has yet been obtained as to this point, but there seems little doubt that, in the case of the salts of certain weak acids and bases, hydrolysis plays some part in the alteration of their specific rotations.

(*f*) *Small Variations in the Atomic Equilibrium of Molecules.*—When the effect of a solvent cannot be due to the formation of a hydrate, it is still possible to explain its action if we suppose that the molecules of the solvent and of the active body influence one another to some extent. It is easy to suppose that the presence of foreign molecules in the immediate neighbourhood of an active molecule might so far affect the latter as to produce a change of position of its atoms in space without the effect being sufficient to destroy the internal stability of the molecule and bring about its disruption. Such an intramolecular change would naturally bring about an effect upon the plane of polarization different from that produced by

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[1] Nernst, *Zeit. physikal. Chem.*, **11**, 345 (1893).

[2] Landolt, *Annalen*, **189**, 311 (1877).

[3] Schneider, *Annalen*, **207**, 257 (1881).

[4] Raýman and Kruis, *Bull. Soc. chim.*, [2] **48**, 632 (1887); Raýman, *Ber.*, **21**, 2050 (1888); Jacobi, *Annalen*, **272**, 175 (1893); Pařížek and Šule, *Ber.*, **26**, 1411 (1893).

[5] Freundler, *Bull. Soc. chim.*, [3] **9**, 683 (1893).

[6] Wyrouboff, *Ann. Chim. Phys.*, [7] **1**, (1894)

the molecule in its normal state; and since the more molecules of solvent present, the greater would be the effect produced upon each active molecule, it is probable that increased dilution would have a corresponding effect upon the specific rotation.

§ II. *THE SPECIFIC ROTATION OF COMPLEX SYSTEMS*

1. Solution of an Active Body in Two Inactive Liquids.—If the change in specific rotation in the first solvent be expressed by:—

$$[\alpha]_1 = a + b_1 q + c_1 q^2$$

and in the second solvent by:—

$$[\alpha]_2 = a + b_2 q + c_2 q^2$$

where a is approximately the same in both cases, then the effect of a mixture of the two, provided there be no decrease in volume due to the mixing, will be:—

$$[\alpha] = a + (b_1 p_1 + b_2 p_2)q + (c_1 p_1 + c_2 p_2)q^2$$

where one part by weight of the mixed solvents contains p_1 parts of one component and p_2 parts of the other; and a hundred parts by weight of the solution of the active substance contains q parts of the mixed solvents.

In cases where the substances mix with contraction, some correction for this must be applied.

2. Mixture of Two Active Liquids.—If we assume that the two substances when mixed have no action on each other's specific rotation, then, if the mixture is made up of p_1 parts by weight of a body with specific rotation $[\alpha]_1$, and p_2 parts of a body with rotation $[\alpha]_2$, the rotation of the mixture will be:—

$$[\alpha] = \frac{p_1[\alpha]_1 + p_2[\alpha]_2}{p_1 + p_2}$$

3. Solutions of Two Active Bodies in an Inactive Liquid.—If the mixture contains A_1 per cent. by weight of the first active substance, A_2 per cent. of the second, and F per cent. of

the inactive liquid, and if the effect of the solvent upon the first active body be expressed by the equation :—

$$[\alpha]_1 = a_1 + b_1p + c_1p^2$$

and on the second by :—

$$[\alpha]_2 = a_2 + b_2p + c_2p^2$$

where p is the percentage of active substance in each solution, then by substituting in these equations the values of p expressed in terms of A and F, we find that the rotation of the mixture of the three substances is expressed by :—

$$[\alpha] = \frac{A_1[\alpha]_1 + A_2[\alpha]_2}{A_1 + A_2}$$

4. **Presence of Inactive Bodies.**—When an inactive substance is added to a solution of an active body, an alteration will take place in the specific rotation of the latter, due to changes in chemical equilibrium, the amount of dissociation, or the formation of new compounds. For example, in some cases the addition of weak acids or bases has the effect of increasing the rotatory power to a considerable extent. Biot, in 1837, found that boracic acid affected the rotatory power of tartaric acid; Vignon[1] noticed that the addition of borax to a solution of mannite increased the rotation; while later Fischer[2] observed a similar effect with the pentites and hexites discovered by him. This effect is sometimes utilised to render the detection of a very small rotation more easy. Acid molybdates, tungstates, and arsenates act similarly.

From the observations of Magnanini,[3] it appears that in the case of borax and mannite, for instance, actual combination takes place between the two substances. It is noteworthy that these phenomena are only noticed in the cases of polyhydroxy compounds such as poly-alcohols and hydroxy-acids;

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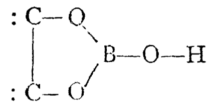
[1] Vignon, *Compt. rend.*, **77**, 1191 (1873); *Ann. Chim. Phys.*, [5] **2**, 440 (1873).

[2] Fischer, *Ber.*. **23**, 385 (1890).

[3] Magnanini, *Gazzetta*, **20**, 428 (1890); **21**, 134 (1891); *Zeit. physikal. Chem.*, **6**, 58 (1890).

and from this it seems not improbable that some cyclic compound is produced. Further, though borax itself has an alkaline reaction, an addition of it to a sugar solution produces a mixture having a strongly acid character. The following formula has been put forward by van't Hoff[1] as a possible method of combination :—



Weber and McPherson[2] found that the rotatory power of certain substances was altered by the presence of large quantities of hydrochloric acid, sodium carbonate, and acetic acid. Papers by other workers[3] in the same field may be consulted.

From an examination of the elements whose compounds have the effect of increasing the rotatory power :—

II.	III.	IV.	V.	VI.
Be	B	Ti	As	Mo
		Zr	Sb	W
				U

Walden[4] deduces that the maximum action is produced by the elements of the sixth group in the periodic system,

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[1] Van't Hoff, *The Arrangement of Atoms in Space*, p. 151.

[2] Weber and McPherson, *J. Amer. Chem. Soc.*, **17**, 312, 320 (1895).

[3] Gernez, *Compt. rend.*, **106**, 1527 (1888) ; **108**, 942 ; **109**, 151 (1889) ; **110**, 529 ; **111**, 792 (1890) ; **112**, 226 (1891). Long, *Amer. J. Sci.*, [3] **40**, 275 (1890). Pribram, *Zeit. anal. Chem.*, **30**, 313 (1891). Haller, *Compt. rend.*, **112**, 144 (1891). Farnsteiner, *Ber.*, **23**, 3570 (1890). Bremer, *Rec. trav. chim.*, **6**, 255 (1887). Pottevin, *J. Physique*, [3] **8**, 373 (1899). Walden, *Ber.*, **30**, 2889 (1897). Grossmann and Potter, *Ber.*, **38**, 3874 (1905). Henderson, Orde, and Whitehead, *Trans.*, **75**, 542 (1899). Henderson and Prentice, *Trans.*, **83**, 259 (1903). Milroy, *Zeit. physikal. Chem.*, **50**, 443 (1905). Grossmann, *Zeit. Ver. deut. Zuckerind.*, **1905**, 650. Rosenheim and Itzig, *Ber.*, **33**, 707 (1900). Itzig, *Ber.*, **34**, 2391 (1901). Grossmann and Potter, *Zeit. physikal. Chem.*, **56**, 577 (1906).

[4] Walden, *Ber.*, **38**, 345 (1905).

PART II.—STEREOISOMERISM WITHOUT OPTICAL ACTIVITY.

CHAPTER I.

CIS–TRANS ISOMERISM IN CYCLIC COMPOUNDS.

§ I. *THE GENERAL THEORY OF THE CONFIGURATION OF SATURATED CYCLIC COMPOUNDS.*

In a previous chapter it was mentioned that in some cyclic compounds which contain more than one asymmetric carbon atom, the difference between the two isomeric forms is greater than that observed in the case of open-chain substances; and this was attributed to the ring-formation tending to limit the vibration spheres of the various atoms in a cyclic compound to a greater extent than is observed in an open-chain substance. The difference between the two classes of compounds is shown to a marked degree in certain cases with which the present chapter will deal. It is found that two isomeric compounds can exist, whose structures are identical; while the one compound possesses the property of undergoing certain intramolecular reactions which cannot be produced in the second isomer. This difference can be explained if we assume that in the former case some atoms lie near one another, while in the latter case they are placed so far apart in space as to be unable to affect each other chemically. In the open-chain compounds such phenomena rarely occur, but in the cyclic series they are common. It is therefore clear that the formation of the ring has produced a considerable change in the properties of the substances.

By applying the same principles as in the case of the configuration of the molecule MR_4, it can be shown that the centres of the carbon atoms of a carbocyclic compound lie in one plane, since this arrangement would produce the least deviation from the normal positions of equilibrium of the atoms.

The case is not altered if an oxygen or other atom be introduced instead of one of the carbon atoms, as in the case of ethylene oxide :—

$$\begin{array}{l} CH_2\diagdown \\ |\qquad O \\ CH_2\diagup \end{array}$$

Now, if we consider the case of trimethylene, it is evident that the atoms are grouped in three sets, each in a different plane, and all three planes being parallel to each other. The carbon atoms lie in one plane, while on either side of this lies a plane containing three hydrogen atoms :—

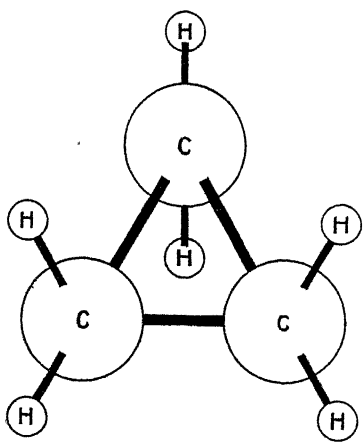
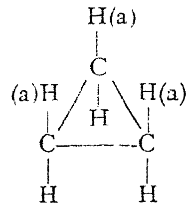


FIG 27

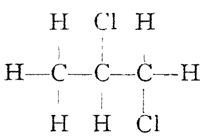
It would be clumsy to use the tetrahedron or the sphere as

a symbol in every case; to avoid this, therefore, formulæ are used which express the same idea :—

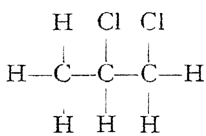


The three hydrogen atoms marked (a) are supposed to lie above the plane of the ring, while the other three lie beneath it.

When we come to the question of substitution, it is evident that we are now dealing with a case very different from that of an open-chain compound. If we consider the case of *αβ*-di-chloro-propane, for instance, we may write it either as (I.) or as (II.):—



(I.)

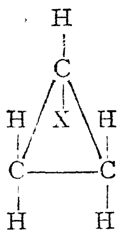
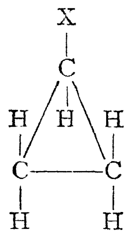


(II.)

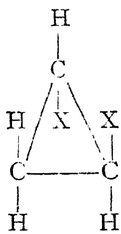
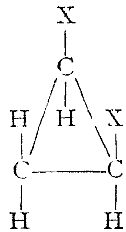
There is no difference between the two substances, as (I.) may be converted into (II.) by a mere rotation of the right-hand carbon atom. When we come to deal with a cyclic compound, however, the case is altered; for here rotation cannot take place without disturbing the whole equilibrium of the ring. But since the atoms of the cyclic molecule are supposed to be in the most stable positions, such a disturbance would need to be so violent that, except in extreme cases, the molecule would be disrupted by it.

In a cyclic compound, therefore, we can foresee two substitution products which will be structurally identical while differing in the space arrangements of the atoms in the molecule. But this will not occur in all cases; for the two compounds shown below, though at first sight different, are really

the same, as can be seen by turning one upside down, when it will be found to be identical with the other.

The first instance of the spacial isomerism occurs in the case of a di-substituted compound :—

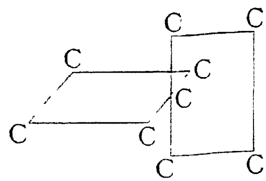
 

In the above figures there is no possibility of making the first coincide with the second by any turning of the paper, for in the first case the two X groups lie in different planes, while in the second they are in the same plane. Partially unsaturated rings also are capable of giving rise to the same kind of isomerism.

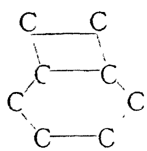
In order to distinguish one isomer from the other, the following nomenclature is usually adopted. When the two substituents lie in the same plane they are said to be in the *cis-position* to one another; when they lie in different planes they are said to be in the *trans-position* to each other.

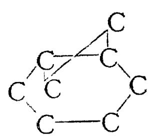
It will be convenient to deal at this point with the configurations of di-cyclic compounds. There are three chief cases

1. *Systems having One Atom in Common.*—In this case the two rings lie at right angles to one another :—

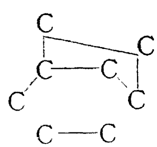


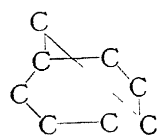
2. *Systems having Two Atoms in Common.*—Here there are two possible cases ; for the two rings may either meet at an angle, or cross one another :—





3. *Systems having more than Two Atoms in Common.*—Here again there are two possibilities, for just as in the last case, the second ring may be joined to two affinities lying on the same side of the carbon ring, or to two on opposite sides.



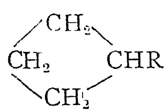


It is apparent that the "crossed" rings will only be stable in very exceptional circumstances, as their formation will divert the atoms very far from their most stable positions.

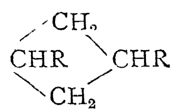
§ II. *DIFFERENCES IN THE CONFIGURATIONS PRODUCED BY SUBSTITUTION.*

The case in which substitution in a saturated cyclic compound gives rise to an asymmetric carbon atom has already been dealt with; in the present section another type of asymmetry will be described. If we have a ring-compound such as tetramethylene, it is obvious that the introduction of a single substituent will not produce real asymmetry; but if into this mono-substituted product we introduce a second substituent, asymmetry might be created. Now, the introduction of this second substituent may take place in either of two ways: either the resulting compound is symmetrically substituted, or it is not. Since these cases differ to a considerable extent from one another, it will be well to deal with them in turn. We shall deal first with symmetrical substitution.

If we take any cyclic compound, such as tetramethylene, and introduce a single substituent into it, the molecule becomes unsymmetrical (I.); and in order to restore symmetry, a second substituent must be introduced in such a way that the line joining the two substituents becomes a line of symmetry of the molecule (II.). Of course, at present we are dealing only with *structural* symmetry.



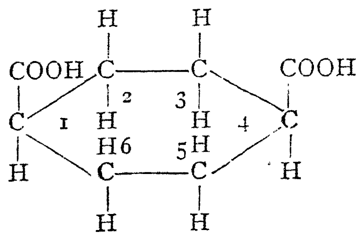
(I.)



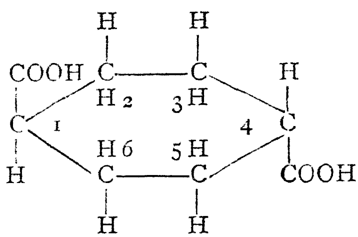
(II.)

Here there is no possibility of a structurally asymmetric carbon atom being formed; but, as we have already shown, there is another form of isomerism which may make its appearance at this stage. The case of the hexahydro-terephthalic acids furnishes the best example. It has been treated

by von Baeyer,[1] from whose paper the next paragraph is quoted.



(I.)



(II.)

"Suppose that the body of an observer lies in the plane of the ring (Formula I.) his feet being at (1), his head at (2), and his face turned away from the centre of the ring. If he now swims along the ring until his head reaches (4), he will see the carboxyl group above him to his left hand, the H (4) atom being to his right. If, on the other hand, he had left the carbon atom (1) in the opposite direction, but in the same position—his feet at (1) and his head at (6), while his face was again turned away from the centre of the ring—he would perceive, on arriving at (4), that the carboxyl was on his right, and H (4) on his left, that is to say, the reverse of the last appearance. From this it follows that the two affinities of the carbon atom (1), which serve to form part of the ring, are not similarly bound; and therefore the carbon atom (1) is

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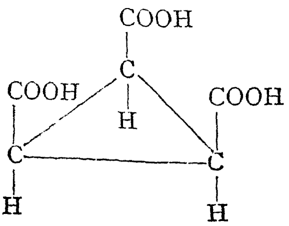
[1] Baeyer, *Annalen*, **245**, 128 (1888).

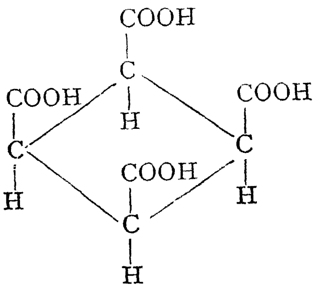
asymmetric. The same relations hold good if one sets out from the carbon atom (4) either to right or left toward (1) Formula (I.), therefore, contains two asymmetric carbon atoms, (1) and (4). The same is true for Formula (II.)."

Of course, this is really a special case of pseudo-asymmetry; but here the asymmetries of the two carbon atoms are inter-dependent, for if the carboxyl group attached to one carbon atom be replaced by hydrogen, the asymmetry of both carbon atoms is destroyed. On this account, von Baeyer gave to such cases the designation *Relative Asymmetry*.

The number of relatively asymmetric carbon atoms in a cyclic molecule can be increased by the further symmetrical introduction of substituents. For instance, in Formula (I.) below, there are three relatively asymmetric carbon atoms, and Formula (II.) contains four of them:—



(I.)



(II.)

Since each pair of relatively asymmetric carbon atoms gives rise to two isomers, the number of possible isomers in any case is equal to the n^{th} power of 2, where n is the integral part of the number produced by halving the number of relatively asymmetric carbon atoms in the compound. For instance, where there are four relatively asymmetric carbon atoms:—

$$\frac{4}{2} = 2\text{; therefore number of isomers is } 2^2 = 4$$

Where there are seven relatively asymmetric carbon atoms:—

$$\frac{7}{2} = 3\tfrac{1}{2}\text{; therefore number of isomers is } 2^3 = 8$$

The following table gives the number of isomers for compounds containing from one to eight relatively asymmetric carbon atoms :—

Relatively asymmetric carbon atoms.	Number of possible isomers.
2	2
3	2
4	4
5	4
6	8
7	8
8	16

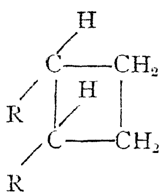
To simplify the representation of these isomers, Aschan's method, already described, may be used.*

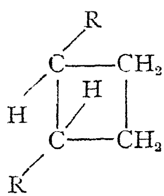
In its main lines, the case of unsymmetrical substitution does not differ from that of symmetrical substitution.

$$\begin{array}{ccc} CH_2 & - & CHR \\ | & & | \\ CH_2 & - & CHR \end{array} \qquad\qquad \begin{array}{cccc} & CH_2 & - & CH\,.\,R \\ & | & & | \\ R\,. & CH & - & CH_2 \end{array}$$

(I.) (II.)

The compound (I.) will exist in the two forms shown below, just as the symmetrically substituted one (II.) does.





The case is more complicated than the previous one, however, for in this compound two of the carbon atoms are structurally asymmetric, instead of being pseudo-asymmetric. This can be

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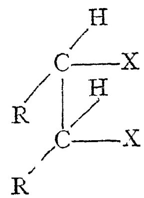
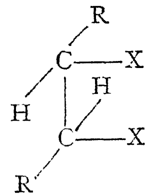
* See p. 77.

seen at once if we replace the $—CH_2—CH_2—$ radical by X in the above cases :—



(I.)



(II.)

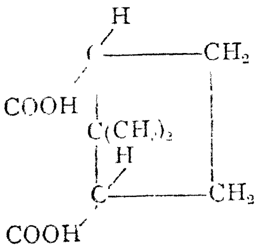
An examination of the last two formulæ shows that they represent a type of compound similar to the tartaric acids, the formula (I.) being the meso-form, while the other represents one of the active isomers. If the two radicals R be different, there will be two active cis-forms which will be optical antipodes. The number of possible isomers may in these cases be reckoned by the usual method for compounds with true asymmetric carbon atoms.

§ III. *THE DETERMINATION OF THE CONFIGURATION OF CIS-TRANS ISOMERS.*

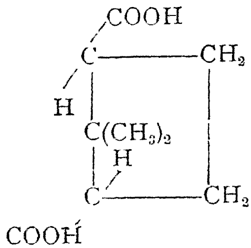
If, in a molecule, we have two radicals capable of reacting upon one another, it is clear that the ease with which the intramolecular reaction takes place depends to a great extent upon the actual distances between the two radicals concerned: for two atoms which are near together are more likely to come within each other's radius of action than they would were they far apart.

If we now consider the case of a cyclic compound which is capable of giving rise to cis-trans isomerism, it is evident that intramolecular reactions will take place more readily when the reacting groups are in the cis-position to one another than when they are in the trans-position; and in some cases it may be easy to produce a reaction in the cis compound which is

impossible in the case of the trans-isomer. For example, camphoric acid exists in two forms: that corresponding to Formula (I.) yields an anhydride, the other (II.) gives the same anhydride, but only with much greater difficulty.[1]

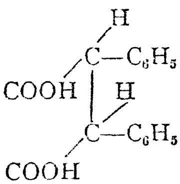


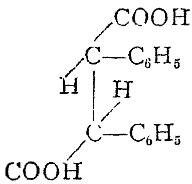
(I.)



(II.)

That this phenomenon is due to the comparative rigidity introduced into the molecule by the cyclic structure can be shown by comparing the above case with that of the diphenyl-succinic acids, where the radical —CH_2—CH_2— is replaced by two phenyl groups. Here it is found that two isomeric anhydrides are formed which can easily be converted into one another.[2]





In the case of cyclic compounds, the change of one anhydride into another is confined to a very few instances; *e.g.* the hexahydro-phthalic anhydrides,[3] and the anhydrides of the two stereo-isomeric pentamethylene-1,2-dicarboxylic acids.[4]

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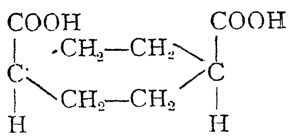
[1] Aschan, *Ber.*, **27**, 2001 (1894).

[2] Tillman, *Annalen*, **258**, 90 (1890); Anschutz and Bendix, *Annalen*, **259**, 61 (1890).

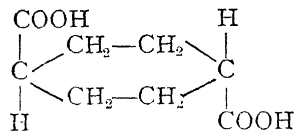
[3] Werner and Conrad, *Ber.*, **32**, 3046 (1899).

[4] Perkin, *Trans.*, **65**, 582 (1894).

It will not be necessary to enter into many details as to the application of this method of configuration determination: one example will suffice. It is found that there are two stereoisomeric hexahydro-terephthalic acids, one of which easily gives an anhydride, while the other will not give any. This is attributed to the fact that in the one case the carboxyl groups lie on the same side of the ring, while in the second compound they are in the trans-position to one another.

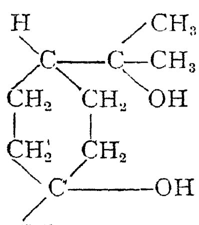


Gives anhydride.

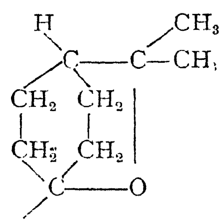


Gives no anhydride.

The non-formation of an anhydride in the case of the trans-acid is very noteworthy, as it is not an uncommon thing to find intramolecular ring-formation between the para-positions, as, for instance, in the case of the conversion of cis-terpin into cineol.[1]



Cis-terpin

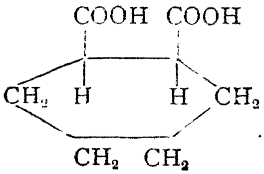


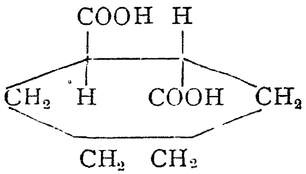
Cineol

It has already been stated that cis-trans isomers containing two structurally similar carbon atoms which are also truly asymmetric, can be distinguished from one another by their different effects upon the plane of polarization; for the trans-compound will correspond to a racemic substance, while the cis-isomer will be similar to an intramolecularly compensated

[1] Baeyer, *Ber.*, **26**, 2866 (1893).

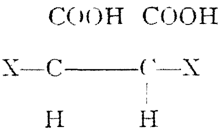
variety. This has been proved by Werner and Conrad[1] for the case of the hexahydro-phthalic acids: they resolved the trans-compound, but failed to obtain an active form of the cis-isomer.

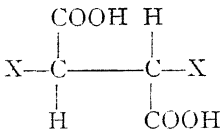




Cis-compound corresponding to the meso-form.

Trans-compound corresponding to the active form.





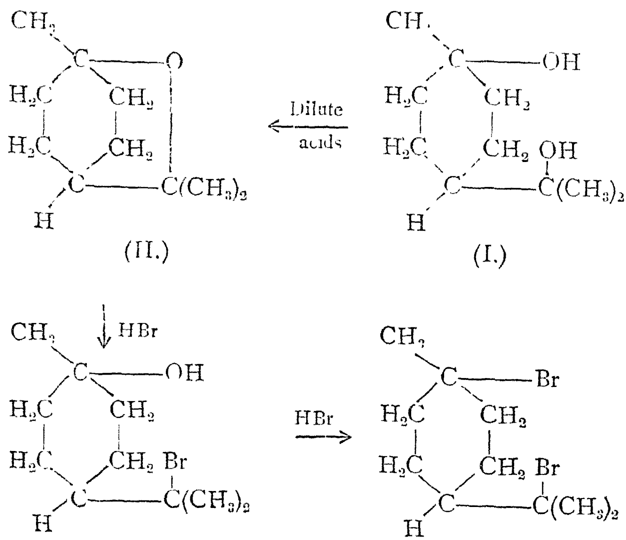
The results obtained in this way agreed with those deduced from anhydride formation; the substance having the higher melting-point being designated as the trans-isomer by both methods.

When no intramolecular ring-formation can be brought about in two isomers, the configuration cannot be determined with any certainty; but a very probable surmise may be made from the evidence furnished by the melting-points of the two isomeric compounds. In general, it has been observed that the trans- compound has a higher melting-point than the cis-isomer, so that where the configuration is doubtful, this test may be applied. Too much reliance cannot be placed upon it, however, for cases are known in which the cis-compound has the higher melting-point of the two.

In a few isolated cases it is possible to synthesise two new stereoisomeric substances from two stereoisomers whose configurations have already been determined; and in this way

[1] Werner and Conrad, *Ber.*, **32**, 3046 (1899).

the configurations of the new isomers may be deduced, if we assume that no change in configuration has been brought about during the reactions which lead from the first pair of compounds to the others. For example, we have already mentioned that cineol (II.) may be obtained from the compound cis-terpin (I.), which has a similar configuration. Now, when cineol is treated with hydrobromic acid, under conditions which do not encourage transmutation, it is converted into a bromohydrin whose configuration must be represented by (III.); this bromohydrin is converted almost immediately into the di-hydrobromide (IV.), which also must have the cis- configuration. We have thus been able to deduce the configuration of this final product from our knowledge of the configuration of the original cis-terpin.



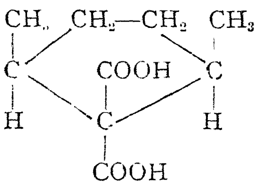
(II.) (I.)

(III.) (IV.)

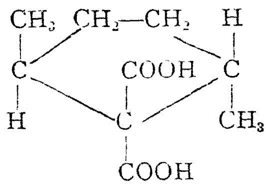
When a symmetrical compound is converted into a less symmetrical one, the number of possible cis-trans isomers is increased; and from the relations between the original

compounds and their products it is possible to gain some insight into the configurations of the former substances.

Wislicenus[1] was able to determine in this way the configurations of the two stereoisomeric 2,5-dimethyl-cyclopentane dicarboxylic acids. The two isomers which were synthesised had configurations corresponding to the formulæ :—

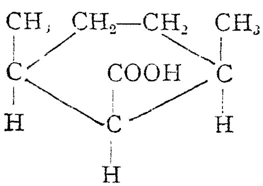


Cis-dimethyl acid.

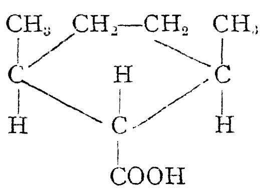


Trans-dimethyl acid.

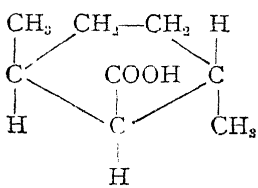
Now, when one carboxyl group is split off from each acid, three forms in all are possible for the new mono-carboxylic acid :—



(I.)



(II.)



(III.)

Inspection will show that the acids (I.) and (II.) are derivatives of the cis-dimethyl acid, while (III.) can be produced from

[1] Wislicenus, *Ber.*, **34**, 2565 (1901).

the trans-isomer. It was shown by Wislicenus that the facts agree with the theory; for one of the dicarboxylic acids (M.P. 192–194° C.) yields on heating a mixture of two acids (M.P. 75–77° and 26–30° C.). It is therefore the cis-dimethyl acid. The other dicarboxylic acid (M.P. 204–205° C.) yields when heated only one acid (M.P. 49·5° C.). It is therefore the trans-dimethyl dicarboxylic acid.

A similar principle was used in an attempt to determine the configuration of the trithioaldehydes,[1] but it was not successful owing probably to the chemical nature of the groups involved.

§ IV. *THE PROPERTIES OF CIS-TRANS STEREOISOMERS.*

1. Physical Properties.—It appears that though in the greater number of the cases known the trans-isomer has the higher melting-point of the two, yet there is a series of exceptions to this rule which deserves consideration. The following table will be sufficient to serve the present purpose:—

Name.	Cis-.	Trans-.
Trimethylene-1,2-dicarboxylic acid	139° C.	175° C.
Trimethylene-1,2,3-tricarboxylic acid	150–153°	220°
Trimethylene-1,1,2,3-tetracarboxylic acid	95–100°	191–192°
*Tetramethylene-1,2-dicarboxylic acid	137–138°	131°
Tetramethylene-1,3-dicarboxylic acid	135–136°	170–171°
Pentamethylene-1,2-dicarboxylic acid	140°	159–160°
*Pentamethylene-1,3-dicarboxylic acid	120–121°	87–88°
Hexahydrophthalic acid	192°	215°
*Hexahydro-isophthalic acid	161–163°	118–120°
Hexahydro-terephthalic acid	161–162°	300°
*Camphoric acid	187°	171–172°

An examination of the figures shows that those trans-forms (marked with an asterisk in the table), which have a lower melting-point than the isomeric cis-forms, have the carboxyl groups in the 1,3-position to one another. Now, on comparing

[1] Baumann, *Ber.*, **24**, 1425 (1891).

the melting-points of open-chain dicarboxylic acids, we find that acids containing an *uneven* number of carbon atoms have lower melting-points than those with a carbon atom more or less:—

		Melting-point
$(COOH)_2$	Oxalic acid	189° C.
$CH_2(COOH)_2$	Malonic acid	132°
$(CH_2COOH)_2$	Succinic acid	185°
$CH_2(CH_2COOH)_2$	Glutaric acid	97°
$(CH_2CH_2COOH)_2$	Adipic acid	148°
$CH_2(CH_2CH_2COOH)_2$	Pimelic acic	106°
$(CH_2CH_2CH_2COOH)_2$	Suberic acid	140°

It will be shown later that some open-chain dicarboxylic acids probably exist in the trans-form,* so that there appears to be some connection between the cases given in the two tables. This idea was put forward by Werner.[1] His interpretation, however, is not very convincing, for the same alternate rise and fall in melting-point is shown by the monobasic fatty acids, in whose case no space considerations seem called for.

With very few exceptions it appears that those isomers having the higher melting-point are the less soluble of the two.

Δ^4-Tetrahydrophthalic acid—

M.P. 215°–218° C.	sol. in	690	parts H_2O	at	6° C.
M.P. 174° C.	,,	108	,,	,,	,,

$\Delta^{3,5}$-Dihydrophthalic acid—

M.P. 210° C.	sol. in	610	parts H_2O	at	10° C.
M.P. 173°–175° C.	,,	93	,,	,,	,,

The specific gravity and crystalline form appear to be different in the case of each isomer.

As might be anticipated, the cis-compounds usually have a higher affinity constant than the trans-isomers.[2] They are therefore stronger acids. An exception is to be found in the

* See Section II., Chap. IV.

[1] Werner, *Lehrbuch der Stereochemie*, p. 173

[2] Bone and Sprankling, *Trans.*, **83**, 1378 (1903).

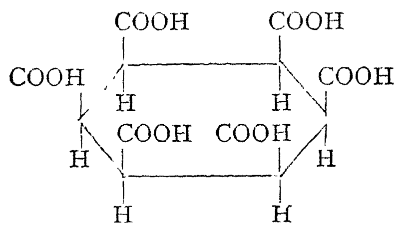
case of the 1,2-hexahydrophthalic acids, where the trans-form has the greater affinity constant:—

Cis-form 0·0044 Trans-form 0·0062

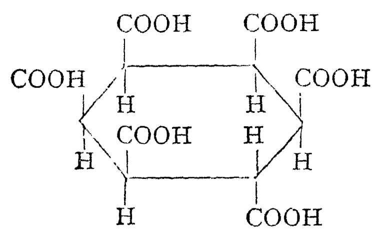
Stohmann and Kleber[1] have found that the heats of combustion of one gramme-molecule of the cis- and trans-forms of hexahydroterephthalic acid differ but slightly from each other:—

Cis-acid 928·6 cal. Trans-acid 929·5 cal.

2. Chemical Properties.—Differences in chemical properties between the two isomers are very strongly marked in cases of intramolecular reactions such as anhydride or lactone formation. These have already been described. A somewhat similar difference has been noticed in the esterification of hydromellitic and iso-hydromellitic acids:—



Hydromellitic acid.



Isohydromellitic acid.

In the case of the normal compound, which has all its carboxyl groups on the same side of the ring, no ester is formed under

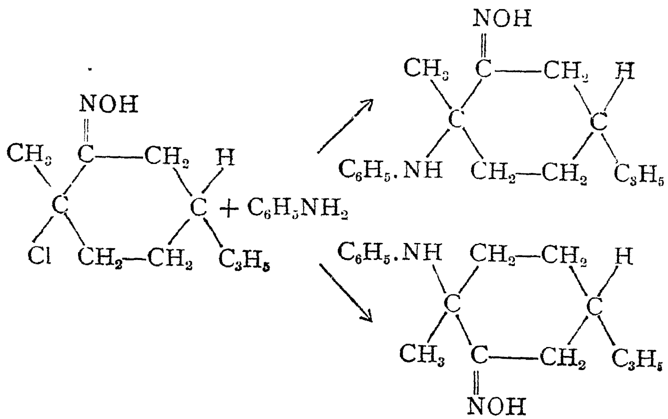
[1] Stohmann and Kleber, *J. pr. Chem.*, [2] 45, 489 (1892).

conditions allowing the esterification of one carboxyl group in the iso-acid, which is supposed to have that carboxy-group on the other side of the ring from the remaining five. Differences have also been observed in the capacity of the two isomers to form addition compounds with solvents.

§ V. *THE TRANSMUTATION OF CIS-TRANS ISOMERS.*

Some isomers, on simple heating, are converted into the other form: *e.g.* cyclopentane-1,3-dicarboxylic acid.[1]

Sometimes when substitution takes place in a cyclic compound the resulting product is a mixture of two isomers; so that part of the original compound is converted into the stereo-isomeric type. For example, the action of aniline upon limonene α-nitroso-chloride takes place according to the equation below:[2]—



Similar phenomena of transmutation are observed when transhexahydro-terephthalic acid is brominated, the result

[1] Pospischill, *Ber.*, **31**, 1952 (1898).
[2] Wallach, *Annalen*, **252**, 113 (1889).

being a mixture of the cis- and trans-forms of dibromo-hexa-hydro-terephthalic acid.[1] The reverse process, reduction of the cis- or trans-dibromo-compound produces a mixture of the cis- and trans-hexahydro-terephthalic acids.[2]

Bases and acids have in some cases the power of transmuting the one isomeric form into the other. Fusion with caustic potash changes β-truxillic acid into the δ-form;[3] lævo-ecgonine on boiling with potassium hydroxide yields dextro-ecgonine.[4] When heated with mineral acids the cis-forms of the following acids are converted into the trans-isomers: the tetramethylene dicarboxylic acids;[5] pentamethylene-1,2-dicarboxylic acids;[6] and hexahydromellitic acid.[7]

In some cases, transmutation takes place in presence of acetyl chloride or halogens; *e.g.* α-trithio-acetaldehyde is changed into the β-variety by a trace of iodine.[8]

Some isomers can be transmuted into the other form by using the formation of an intermediate compound as a step in the process. For instance, a trans-dicarboxylic acid may be converted into a cis-anhydride, and this in turn into the cis-acid.

The action of aqueous solutions of acids at high temperatures in sealed tubes has been studied sufficiently to enable us to draw certain conclusions with regard to various dicarboxylic acids of the alicyclic series. It is found that stereoisomeric 1,2-dicarboxylic acids have different stabilities; the cis-form, being the less stable, is converted into the trans-form. The stereo-isomeric 1,3-dicarboxylic acids appear to be almost equally stable when heated with acids in sealed tubes. From the behaviour of the hexahydro-terephthalic acids it may be concluded that they resemble the 1,2-acids.

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[1] Baeyer, *Annalen*, **245**, 103 (1888).
[2] Ibid.
[3] Liebermann, *Ber.*, **22**, 2250 (1889).
[4] Einhorn and Macquardt, *Ber.*, **23**, 469, 979 (1890).
[5] Perkin, *Trans.*, **65**, 585 (1894).
[6] Ibid.
[7] Baeyer, *Ber.*, **1**, 118 (1868).
[8] Baumann and Fromm, *Ber.*, **24**, 1457 (1891).

By a combination of the methods mentioned above, it is ossible to pass from one isomer to the other and back to the riginal one again. The case of the hexahydro-phthalic acids rnishes a good example of this cyclic process:—

$$\begin{tikzcd}[column sep=huge, row sep=large]
\begin{array}{c}\text{Cis-hexhydrophthalic acid}\\ \text{(M.P. } 215^\circ \text{ C.).}\end{array} \arrow[r, "\text{Heating with HCl}"'] \arrow[d, shift right=2, "CH_3COCl"'] & \begin{array}{c}\textit{dl-}\text{ Trans-hexahydrophthalic acid}\\ \text{(M.P. } 215^\circ \text{ C.).}\end{array} \arrow[d, shift right=2] \\
\begin{array}{c}\text{Cis-anhydride}\\ \text{(M.P. } 32^\circ \text{ C.).}\end{array} \arrow[u, shift right=2, "H_2O"'] & \begin{array}{c}\textit{dl-}\text{ Trans-anhydride}\\ \text{(M.P. } 140^\circ \text{ C.).}\end{array} \arrow[l, "\text{Long heating}"'] \arrow[u, shift right=2, "H_2O"']
\end{tikzcd}$$

CHAPTER II.

GEOMETRICAL ISOMERISM IN THE ETHYLENE SERIES.*

§ I. *HISTORICAL.*

IN certain organic derivatives of the ethylene series an isomerism has been observed which is due neither to structural differences nor to the presence of asymmetric carbon atoms in the compounds. Both Le Bel and van't Hoff came to the conclusion that the origin of this isomerism must be sought in the arrangement of atoms in space; and with but few exceptions the facts known to us to-day are capable of explanation on the lines indicated by them. In 1881, van't Hoff, in his *Ansichten uber die Organische Chemie*, called attention to the probability that the formation of anhydrides from dibasic acids, such as phthalic and maleic, depended upon the proximity to one another of the two carboxyl groups concerned in the reaction; and a year later Le Bel,[1] from a study of the oxidation of fumaric and maleic acids, not only came to a similar conclusion, but also indicated the relative positions in space occupied by the carboxyl groups in these two acids. By the year 1887 the subject was so far advanced that Wislicenus[2] published a paper entitled, *The Spacial Arrangement of Atoms*

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* Though some authors have used the term *geometrical isomerism* to denote any form of stereoisomerism, it seems preferable to confine it to that type of stereoisomerism in which the atoms chiefly concerned lie in one plane. The best recommendation for this application lies in the ease with which isomers of the ethylene type are distinguished from active isomers: one word being sufficient instead of a phrase.

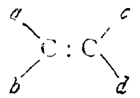
[1] Le Bel, *Bull. Soc. chim.*, [2] **37**, 300 (1882).

[2] Wislicenus, *Abhandl. d. Konigl. sachsischen Gesellsch.*, **14**, No. 1 (1887).

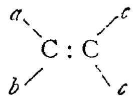
in Organic Molecules and its Determination in Geometrically Isomeric Unsaturated Compounds, in which he developed the theory of this type of isomerism, and put forward a hypothesis to account for the transmutation of one isomer into another. The results of the work done since that time have now to be considered.

§ II. *THE GENERAL CHARACTER OF ETHYLENE ISOMERS.*

In order that geometrical isomerism may be shown in any compound, two conditions must be fulfilled: first, the molecule must contain a double bond between two of its carbon atoms; second, the two monovalent radicals attached to each of these carbon atoms must not be the same. The following formula expresses these two conditions, where *a* is different from *b* and *c* from *d*:—



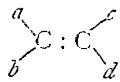
The presence of the double bond is proved to be necessary by the fact that, when two stereoisomers are reduced, the same end-product is formed from both; *e.g.* maleic and fumaric acids both yield the same succinic acid. The necessity of complying with the second condition is shown by the fact that compounds of the type:—



do not occur in two stereoisomeric forms.

From the fact that in any compound, $CR_1R_2R_3R_4$, optical activity was found when the molecule was asymmetric (*i.e.* when R_1, R_2, R_3, R_4 were all different from one another), it was at one

time supposed that a similar activity might be expected in the case of molecules of the type :—



where asymmetry also occurs, though it is of a different class. In order to test this idea, Le Bel[1] carried out a series of experiments in which he endeavoured to isolate active forms of allyl alcohol, α-crotonic acid, fumaric, maleic, citraconic, and mesaconic acids. Similar researches were made by Anschütz[2] and Walden.[3] All were unsuccessful, and to-day it is concluded that optical activity is not occasioned in ethylene isomers unless the compounds in question contain asymmetric carbon atoms of the usual type.

There is no enantiomorphism shown in the crystalline forms of geometrical isomers such as is exhibited by optical antipodes; but, on the other hand, the latter do not show to any marked degree the divergence which is found between many physical and some chemical properties of two geometrical isomers. The physiological actions of two geometrical isomers are also quite different in certain cases.

As a general rule, if the foregoing conditions have been fulfilled, two isomers are found when the compound contains only one double bond. The exceptions to this will be dealt with later. When two or more double bonds are present, there is a corresponding increase in the number of possible isomers; *e.g.* two double bonds would produce as many as four isomers if the structure of the compounds were favourable.

We must now consider the configuration of molecules containing two carbon atoms directly united together. According to our present nomenclature, there are three types of union

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[1] Le Bel, *Bull. Soc. chim.*, **7**, 613 (1892); **11**, 292 (1894); *Compt. rend.*, **114**, 304 (1892).

[2] Anschutz, *Annalen*, **239**, 164 (1887).

[3] The reference to Walden's work is in a letter to van't Hoff mentioned by Werner, *Lehrbuch der Stereochemie*, p. 181.

between carbon atoms: the single (or ethane) bond; the double (or ethylene bond): and the triple (or acetylene) bond. They are usually written $\equiv C.C\equiv$; $>C:C<$; $-C\equiv C-$. We may deal with them in the above order.

1. The Single Bond.—If for the sake of simplicity we assume the form of the carbon atom to be a regular tetrahedron, then two atoms united by a single bond will be represented as in Fig. 28. Now, if we consider the case of such a compound as ethylene dichloride, $CH_2Cl.CH_2Cl$, we see that it may be expressed in the tetrahedral formula by three different arrangements. In Fig. 29, the upper tetrahedron has been kept in the same position throughout the three cases, while the order in which the atoms are distributed round the lower tetrahedron varies in each case. Hence we might expect to find three isomeric dichlorethylenes, each corresponding to one of the above formulæ. In practice, however, no such isomerism exists, and only one compound of the formula $CH_2Cl.CH_2Cl$ is known. The tetrahedral formula has therefore been modified by the assumption that when two carbon atoms are united by a single bond, they can

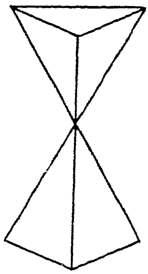


FIG 28

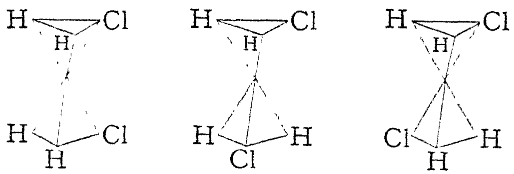
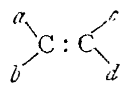


FIG 29.

rotate freely about their common axis. On this hypothesis the three formulæ of Fig. 29 represent merely phases of intramolecular movement, and not actually stable positions of the tetrahedra. This free rotation need not in all cases be a continuous motion; for it may be assumed that the atoms in any compound have a certain influence upon one another,

even if they are not directly united, and that as the result of such influences, there must be one particular arrangement of the atoms which is more stable than any other. In this case also free rotation is assumed, though not continuous rotation; and it is supposed that if the atoms are arranged in any way whatever, they will spontaneously rearrange themselves into the stable position, and that thereafter any intramolecular movement will take the form of a mere oscillation about the stable position. This latter hypothesis is the more satisfactory of the two, as it explains certain facts known as to the crystallographic relations between some saturated and unsaturated compounds.

2. The Double Bond.—It has already been stated that geometrical isomerism can be expected only in compounds containing the grouping:—



where *a* differs from *b*, and *c* from *d*; and that if this condition be fulfilled, such isomerism will exist even though the compounds be exactly similar to one another in structure. The generally accepted explanation of this phenomenon is arrived at by the supposition that when two carbon atoms are united by a double bond, there is no longer any possibility of their revolving freely with respect to each other, but that instead there are two stable positions in which the atoms may come to rest. In fact, it is concluded that in the ethylene isomers we are dealing with the extreme case of the cis-trans isomerism in ring-compounds, the ring being here formed by the valencies of two carbon atoms instead of a higher number. Several explanations of the stability of the two arrangements of the atoms in geometrical isomers have been put forward; and these we must now examine.

The Tetrahedral Hypothesis.—On this assumption, ethylene would be represented by Fig. 30; and if we consider the case of a symmetrical disubstitution product such as ethylene dicarboxylic acid: COOH . CH : CH . COOH, we find that the

carboxyl groups and hydrogen atoms can be arranged in two different ways at the corners of the tetrahedra; thus producing two systems resembling optical isomers in that they cannot be superposed upon one another, but differing from active antipodes, since the one isomer is not the mirror-image of the other. The weak point of this explanation lies in the fact

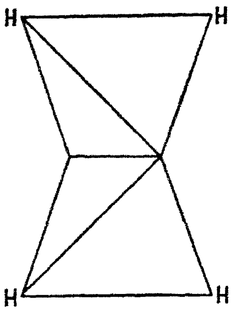


FIG. 30.

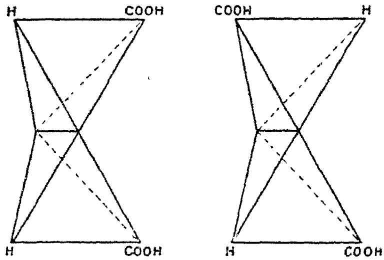


FIG. 31

that it leaves no possibility of one isomer being directly transformed into another without the destruction of the double bond. This will be dealt with later.

(2 *Werner's Explanation.*—It must be clearly borne in mind that Werner, in his explanation,[1] aims at giving nothing more than a symbolical representation of the matter in question. He regards the carbon atom as a sphere whose affinity is distributed evenly over its surface and acts from the centre toward the surface. In the system of atoms:—

$$\begin{matrix} a \diagdown & & \diagup b \\ & C : C & \\ a' \diagup & & \diagdown b' \end{matrix} ,$$

the atoms a, a', b, b', will appropriate to themselves the affinity distributed over the surfaces a and a', b and b' in Fig 32.

[1] Werner, *Beiträge z. Theorie d. Affinität u. Valenz.*, p. 16. See also his *Lehrbuch der Stereochemie*, pp 15, 185

Whatever affinity then remains in the two carbon atoms will be used up in forming the so-called double bond between them; and, as the shading in Fig. 32 shows, this affinity is very characteristically distributed over the surface of both atoms. The portions of affinity of both carbon atoms, which are not situated in the zone of attraction of the atoms a, a', b, b' (*i.e.* the sections marked x in Fig. 33), can saturate each other without in any way hindering the free rotation of the carbon atoms with respect to one another, since this affinity is evenly distributed about their axis of union. On the other hand, those portions marked α in Fig. 33, being irregular in shape,

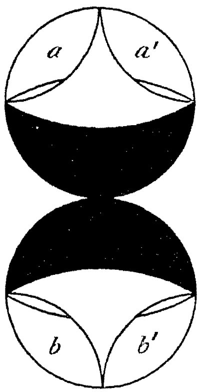


FIG. 32.

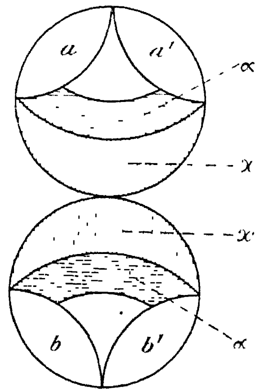


FIG. 33.

can only exert their full attraction upon one another either when the system is in the position shown in the figures, or when one carbon atom has been revolved through an angle of 180°. Hence the most stable positions of the atoms are those shown in the figures. The transmutation of one isomer into the other offers no difficulty on this theory, for since α is only a small fraction of the total affinity of the carbon atoms, it is possible to suppose that heat or other agents might weaken its attractive force to such an extent as to allow transmutation of the labile into the stable isomer to take place.

3. The Triple Bond.—Up to the present time, no case has

been discovered in which stereoisomerism is due to the presence of a triple bond in a compound. It would seem, both from a theoretical and a practical standpoint, that no such isomerism is to be expected in this case.

§ III. *NOMENCLATURE.*

Up to the present, three forms of nomenclature have been brought into common use; and as each has its advantages in certain cases, all three will be utilised in the following pages.

The first form is due to von Baeyer.[1] He proposed to use in all cases the letter *gamma*, with indices to indicate whether similar groups in a compound lay on the same or on opposite sides of the molecule; *e.g.*—

$$\begin{array}{c} \mathrm{COOH{-}C{-}H} \\ \| \\ \mathrm{COOH{-}C{-}H} \end{array} \quad \text{Maleic acid } \Gamma^{\text{cis-cis}}$$

$$\begin{array}{c} \mathrm{COOH{-}C{-}H} \\ \| \\ \mathrm{H{-}C{-}COOH} \end{array} \quad \text{Fumaric acid } \Gamma^{\text{cis-trans}}$$

In modern usage the $\Gamma^{\text{cis-cis}}$ has been simplified to *cis*-, while $\Gamma^{\text{cis-trans}}$ has become merely *cis-trans* or even *trans*.

From the fact that the case of maleic and fumaric acid is so well known, a second type of nomenclature has arisen. Acids having the same configuration as maleic acid are said to belong to the *maleinoid* class, while those resembling fumaric acid are termed *fumaroid* varieties.*

In the third method the cis-cis forms are named *plane-symmetrical*, owing to their having a plane of symmetry in the molecule; the cis-trans form, having no plane of symmetry,

* In consulting the work of Michael, it should be noted that he uses *maleinoid* to designate the isomer with the lower melting-point, and *fumaroid* for the higher melting substance. His use of either term, therefore, does not imply that the *configuration* of the substance corresponds to that of maleic or fumaric acid.

[1] Baeyer, *Annalen*, **245**, 103 (1888).

but being symmetrical about its centre or about an axis drawn through its centre, is called *axial-symmetrical* isomer.

A fourth nomenclature may be mentioned here, though it has not come into general favour. It consists in putting the prefix *allo-* before the name of the compound to indicate the less stable form.

§ IV. *CONFIGURATION DETERMINATION.*

Owing to the structural and constitutional differences between the various compounds which must be classed as geometrical isomers, it has so far been impossible to devise any method of configuration determination which would be applicable to all cases; and even the methods at present at our disposal cannot be said to do more than suggest which of two configurations is the more likely for a given substance.

In the determination of the constitution of any substance, it is always assumed that when the compound undergoes a change, only those atoms which are directly concerned in the action are affected, the other parts of the molecule being supposed to remain unaltered. The same assumption is made in the case of configuration determination, but there it is also assumed that those atoms or atom groups which react with one another are to be found in adjacent positions in space. Neither assumption can be proved at present; and hence there is no certainty that the results obtained by our existing methods are accurate.

There are four chief modes of determining the configuration of ethylene isomers: (1) from their relations to ring-compounds; (2) from their relations to acetylene derivatives; (3) from their relations to ethane compounds; and (4) from the relations between the two ethylene isomers under consideration. These will now be dealt with in turn.

1. Determination of the Configuration from the Relations of Ethylene Stereoisomers to Cyclic Compounds.—This method depends either upon the intramolecular formation of a ring, or upon the breakdown of a ring-compound into an ethylene derivative.

Examples of the first type are to be found in the formation of anhydride from unsaturated dicarboxylic acids such as maleic acid. In the case of the maleinoid compound, in which the two carboxyl groups are situated on the same side of the molecule, the anhydride is easily formed; while in the fumaroid type some difficulty is experienced. A slightly different example is furnished by lactone formation in the case of unsaturated hydroxy-acids. In this case it is assumed that the molecule of water is more readily lost, the nearer together carboxyl and hydroxyl groups lie in the molecule of the hydroxy-acid. The best instance of this kind is to be found in the case of the ortho-coumaric acids. Both are obtained from coumarin, one by simple treatment with alkalis, the other only after long boiling in alkaline solution. The first acid yields coumarin spontaneously, the second does not do so even on heating.[1] The following formulæ illustrate this :—

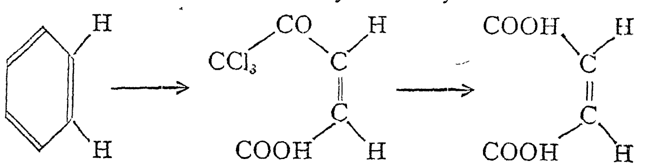
$$\begin{array}{c} \mathrm{H{-}C{-}C_6H_4.OH} \\ \| \\ \mathrm{COOH{-}C{-}H} \end{array} \qquad\qquad \begin{array}{c} \mathrm{H{-}C{-}C_6H_4OH} \\ \| \\ \mathrm{H{-}C{-}COOH} \end{array}$$

Stable acid. Labile acid.

$$\begin{array}{c} \mathrm{H{-}C{-}C_6H_4.O} \\ \| \qquad\quad | \\ \mathrm{H{-}C{-}CO{-}O} \end{array}$$

Coumarin.

In the breakdown of cyclic compounds to ethylene derivatives it is supposed that compounds of the maleinoid type are the end-products of the reaction. When benzene is treated with potassium chlorate and sulphuric acid, it gives trichlorphenomalic acid, which with baryta water yields maleic acid.[2]



[1] Fittig, *Annalen*, **226**, 331 (1884); Wislicenus, *Räumliche Anordnung*, p. 49.

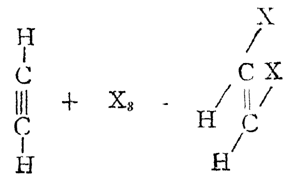
[2] Kekulé, *Annalen*, **223**, 170 (1884).

Similar cases are those of the oxidation of tetrabromo-thiophene to dibromo-maleic acid, and of tribromo-thiotolene to bromo-citraconic acid.

This method of configuration determination is extremely unreliable, owing to the violence of the reactions involved, which might easily bring about a transmutation of the isomer first formed.

2. Determination of the Configuration from the Relations between Ethylene Compounds and those of the Acetylene Series.—Here we may employ either the production of ethylenes from acetylenes, or the reverse process.

The former method, first proposed by Wislicenus,[1] depends upon the assumption that when an acetylene compound is converted into an ethylene derivative the added atoms must take up the cis-position to one another in the new compound.



It cannot be considered a perfectly reliable way of determining configurations, for cases are known (see later) in which addition does not take place in this way, but where the added atoms are found in the trans-position to one another. Further, traces of the halogens have the faculty of causing a transmutation of the unstable isomer into the stable form,* so that it is possible that, though a cis-compound was first formed, it might be immediately converted into the trans-variety. The method can at the best serve only to furnish confirmatory evidence in support of results obtained in some other manner.

In utilising the production of acetylenes from ethylenes for the determination of the configuration of ethylene isomers, the supposition is made that if any ethylene derivative, *a*.X.C:C.*b*.Y,

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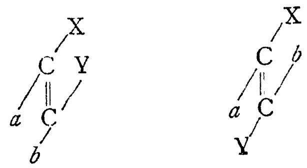
* See § VI., on Transmutation, p. 181.

[1] Wislicenus, *Räumliche Anordnung*, p. 13.

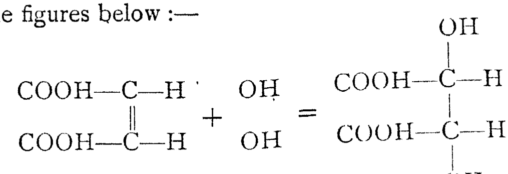
be converted into an acetylenic compound by loss of the groups X and Y, this change will occur more easily the nearer together X and Y lie in the molecule. For instance, in the figures below, the elimination of XY will be easier in (*a*) than in (*b*).



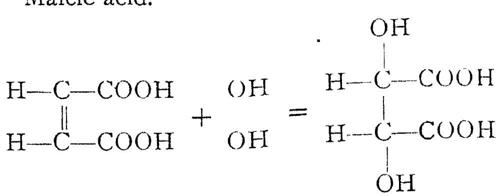
(*a*) (*b*)

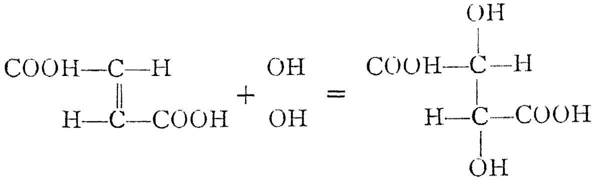
As in the cases of the foregoing methods, too great reliance should not be placed upon the certainty of this.

3. Determination of the Configuration from the Relations of Ethane and Ethylene Compounds.—(*a*) *By changing Ethylenes into Symmetrical Ethanes with Two Asymmetric Carbon Atoms.*—When the two stereoisomeric acids, maleic and fumaric, are oxidised, they yield two different tartaric acids: from maleic acid is derived meso-tartaric acid, which, being inactive owing to internal compensation, cannot be separated into two active isomers; while fumaric acid gives the externally compensated racemic acid, which may be resolved by the usual methods. The reason for this difference can be seen from the figures below:—

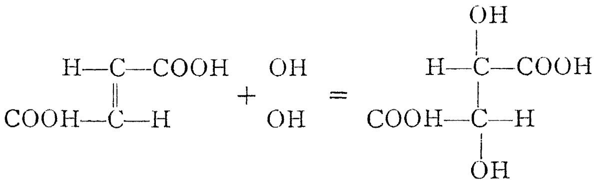


Maleic acid. Meso-tartaric acid.



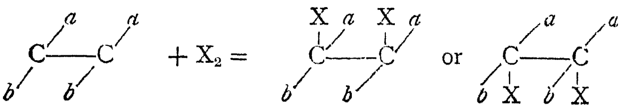


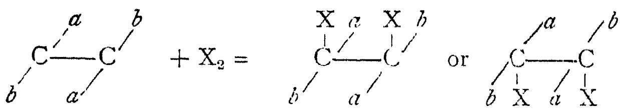
Fumaric acid. *d*-Tartaric acid.



l-Tartaric acid.

From a considerable number of analogous cases it had been deduced that in general a symmetrical ethylene derivative of the cis-form is converted by the addition of two similar atoms, or groups of atoms, into an internally compensated substance, while the trans-form gives rise to the racemic isomer :—

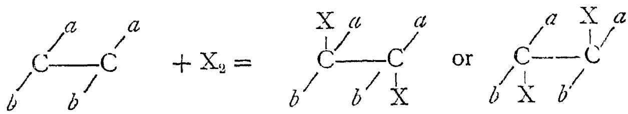




The method, however, cannot be considered wholly reliable, since it assumes that addition always takes place as shown above; while it has been proved by Michael[1] that this is not

[1] See end of this section, p. 171.

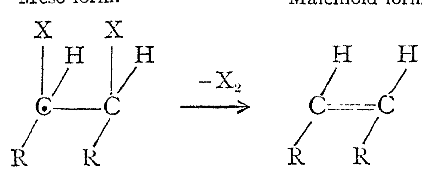
always the case, but that, instead, atoms may be added on according to the scheme below :—

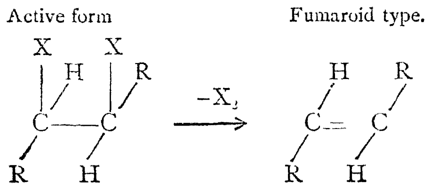


Especially in the case of halogen addition are results obtained in this way to be mistrusted, as several drawbacks can be foreseen. First, the liability of halogens to cause transmutation of one isomer into another may result in such a change happening before any addition-compound is formed; second, even when normal addition has taken place, it may have given rise to a somewhat unstable product, which may then undergo an intramolecular change resembling autoracemisation, and giving rise to a more stable isomer.

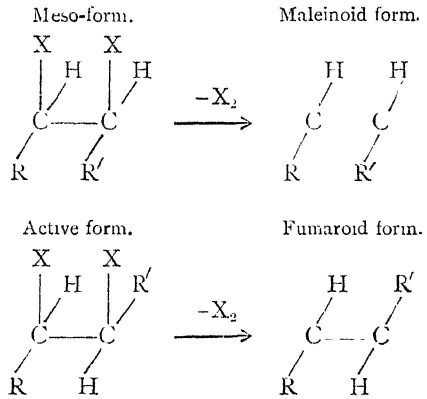
(*b*) *By Transformation of Ethanes into Ethylenes.*—This method in itself is not of any great importance, and is mentioned here merely because it helps to make clearer the relations to be dealt with in the next section. Its basis is somewhat similar to that already mentioned in the case of the conversion of ethylene derivatives into acetylene compounds. As in that instance, it is here assumed that when a compound is converted into a more unsaturated derivative, the operation will be easiest if the eliminated atoms lie near together in the molecule; for example, it was to be expected that when X_2 was lost by the compound R—CHX—CHX—R with two similar asymmetric carbon atoms, the meso- form would give rise to the maleinoid isomer, while the racemic forms would produce the fumaroid type :—

Meso-form. Maleinoid form.





Further, if analogous loss occurred in the case of a compound containing two dissimilar asymmetric atoms (*e.g.* R—CHX—CHX—R′), it was supposed that similar results would be obtained.



These expectations have not been completely fulfilled: for the work of Michael and Schulthess[1] on dibromo-substituted unsaturated acids, as well as Liebermann's[2] on the dibromcinnamic and dibrom-allocinnamic acids has shown that though both isomers are actually produced, the yield of one is extremely small compared with that of the other; a result which does not agree with the deductions made from purely theoretical considerations.

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[1] Michael and Schulthess, *J. pr. Chem.*, [2] **43**, 390 (1891).
[2] Liebermann, *Ber.*, **24**, 1109 (1891).

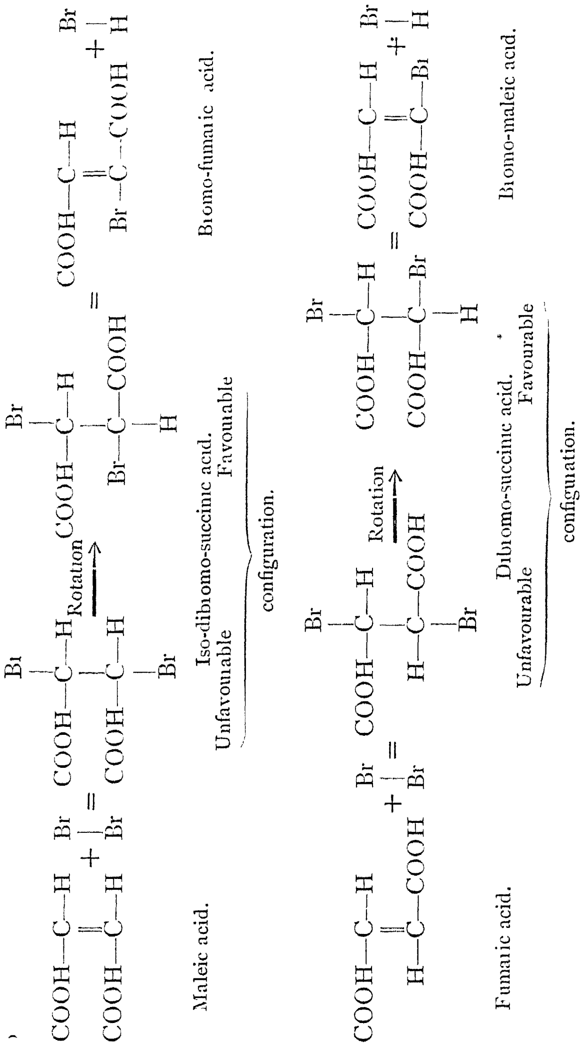
4. Determination of the Configuration from the Relations between Ethylene Compounds.—Certain ethylene stereoisomers have the faculty of adding on various radicals at the double bond, and when the addition-compound so formed is broken down into an ethylene derivative, it is found that a body of different stereoisomeric configuration is produced instead of the original substance. By ascertaining the configuration of the intermediate compound most likely to produce this result, certain deductions may be drawn as to the configuration of the two isomers. For example, maleic acid adds on bromine and yields iso-dibromo-succinic acid, which can be made to lose hydrobromic acid and break down into bromo-fumaric acid; fumaric acid, on the other hand, adds on bromine to form dibromo-succinic acid, which by loss of hydrobromic acid can be converted into bromo-maleic acid. These changes are explained on the assumption that, after addition takes place, a partial revolution of the carbon atoms in the two ethane derivatives is needed to bring their groups into the most stable position. These changes are shown in the table on the next page. Other examples of the same kind will be given later.*

5. Influences which increase the Difficulty of Configuration Determination.—Several of these influences have already been mentioned in the preceding sections. Chief among them is the apparently abnormal addition of halogens to acetylenes to form trans-substituted ethylenes; and the converse case of splitting off atoms which lie in the trans-position to one another. Our knowledge of this branch of the subject is due almost entirely to the work of Michael.[1] Wislicenus[2] had put forward the suggestion that such abnormal additions might be due to intramolecular change taking place after the addition reaction was complete; and he quoted the production of bromo-fumaric acid by the action of hydrobromic acid on acetylene dicarboxylic acid in support of his theory. In his view, two

* See § VII. on Explanations of Transmutation, p. 185.

[1] Michael, *J. pr. Chem.*, [2] **46**, 210 (1892); **52**, 289 (1895).

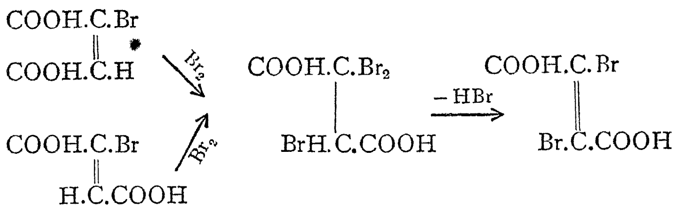
[2] Wislicenus, *Räumliche Anordnung*, p 33.


Maleic acid.
Iso-dibromo-succinic acid.
Unfavourable
Favourable
configuration.
Rotation
Bromo-fumaric acid.
Fumaric acid.
Dibromo-succinic acid.
Unfavourable
Favourable
configuration.
Rotation
Bromo-maleic acid.

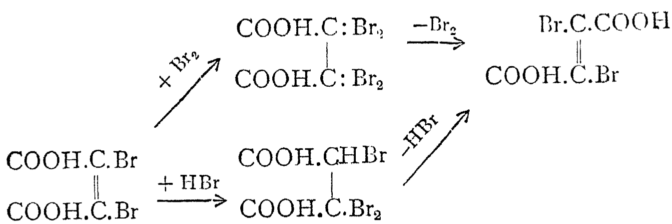
intermediate products were formed: first, monobromo-maleic acid, and then dibromo-succinic acid, which by loss of hydrobromic acid was supposed to be converted into bromo-fumaric acid.

$$\begin{array}{l} \mathrm{COOH.C.Br} \\ \qquad \| \\ \mathrm{COOH.C.H} \end{array} \xrightarrow{\mathrm{HBr}} \begin{array}{l} \mathrm{COOH.C.Br_2} \\ \qquad | \\ \mathrm{COOH.C.H_2} \end{array} \xrightarrow{\text{Rotation and loss of HBr}} \begin{array}{l} \mathrm{COOH.C.Br} \\ \qquad \| \\ \mathrm{H.C.COOH} \end{array}$$

According to this hypothesis, both bromo-maleic and bromo-fumaric acids could be converted into dibromo-fumaric acid by the addition of bromine and loss of hydrobromic acid.



The production of dibromo-fumaric acid may be explained on the same hypothesis in another way. Acetylene dicarboxylic acid gives rise to dibromo-maleic acid in the usual way by the addition of bromine to the triple bond, after which the following changes take place:—



The assumption that bromo-maleic acid can thus be converted into bromo-fumaric acid was proved to be unfounded by Michael,[1] who showed that even when it had stood for days in contact with ten per cent. of hydrobromic acid, no change

[1] Michael, *J. pr. Chem*, [2] **46**, 210 (1892).

occurred. Secondly, acetylene dicarboxylic acid, when treated with hydrobromic acid, does not yield bromo-maleic but only bromo-fumaric acid. And, finally, tribromo-succinic acid, in losing hydrobromic acid, gives rise to a mixture which contains dibromo-maleic acid but no dibromo-fumaric; further, the splitting off of the hydrobromic acid, requires the presence of aqueous alkalis, and does not take place under the conditions furnished by the addition of bromine to acetylene dicarboxylic acid. The Wislicenus hypothesis is thus destroyed, and direct addition in the trans-position seems the only alternative.

Instances such as these, however, are not sufficient to overthrow the whole stereochemistry of the ethylene series. The true solution of the problem is probably to be found in seeking the influences which govern these apparently abnormal cases. Many possible factors could be suggested, such as the mutual influences of the various atoms in the molecule, the effect of physical agencies such as heat or light, the occurrence of secondary reactions or intramolecular changes simultaneously with the addition-reaction, and even chemical influences such as the nature of solvents. A very good example of the effect of such apparently minor influences is furnished by Wislicenus's investigations[1] of angelic and tiglic acids. In his attempts to produce dibromides of these acids he found that quantitative yields were produced only when a large excess of bromine was allowed to act on the acid at low temperatures in total darkness; under other circumstances mixtures of the two isomeric bromides were formed.

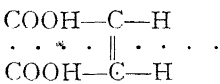
§ V. *THE PROPERTIES OF ETHYLENE STEREO-ISOMERS.*

1. **Physical Properties.**—In 1882 Carnelley[2] stated that of two isomers, that which possessed the most symmetrical and

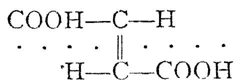
[1] Wislicenus, *Annalen*, **250**, 224 (18`9).

[2] Carnelley, *Phil. Mag.*, [5] **13**, 116 (1882)

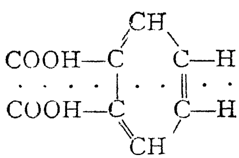
compact structure was distinguished by having the higher melting-point; and Franchimont[1] has brought evidence in favour of this view. Later, Michael,[2] as a result of his work on the unsaturated acids, drew the conclusion that of the two isomers the maleinoid form had the lower melting-point, being also more soluble and volatile. Werner[3] puts forward the idea that this difference in melting-point may be merely one instance of a much more general rule; and quotes as an example the cases of phthalic and terephthalic acids, comparing the ortho-acid with maleic and the para-compound with fumaric acid.



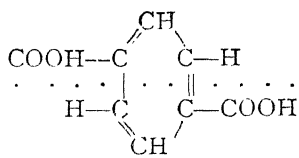
M.P. 130° C.



Sublimes unchanged.



M.P. 213° C.



Sublimes unchanged.

This idea may prove to be based upon mere coincidence, but the fact that benzene para-derivatives have higher melting-points than the corresponding ortho-derivatives seems to point to some general rule such as Werner foreshadows. If such a rule were formulated, it might be of great assistance in determining the configuration of some isomers.

As the experimental material at present available is very limited in extent, no definite conclusions can be drawn as regards the relations of the boiling-points of the isomers; but the indications seem to point to results akin to those noted in the case of the melting-points of cis-trans isomers.

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[1] Franchimont, *Rec. trav. chim.*, **16**, 142 (1897).

[2] Michael, *J. pr. Chem.*, [2] **52**, 345 (1895).

[3] Werner, *Lehrbuch der Stereochemie*, p. 211.

The melting-points and solubility of stereoisomers seem to be connected in some way, as it is found that the isomer with the higher melting-point is always the less soluble of the two. The parallel with the *o*- and *p*-derivatives of benzene is therefore very close in this case also. See also the work of Vaubel.[1] A few instances may be given here :—

Maleinoid.		Approximate solubility.	*Fumaroid.*		Approximate solubility.
Name.	M.P.		Name.	M.P.	
Maleic acid [2] . .	130°	1 : 2 H_2O	Fumaric acid .	—	1 : 150 H_2O
α-Chlorcinnamic [3]	111°	1 : 312 H_2O	α-Chlorcinnamic	137°	1 : 4230 H_2O
β-Chlorcinnamic [3]	133°	1 : 2789 H_2O	β-Chlorcinnamic	158.5°	1 : 5396 H_2O
Citraconic [4] . .	91°	1 : 0·42 H_2O	Mesaconic acid	202°	1 : 38 H_2O

Very little work has been done on the specific gravities of these isomers, but from the results obtained up to the present it appears that the compound with the higher melting-point or boiling-point usually has the higher density;[5] *e.g.* maleic acid has $\delta = 1·590$; fumaric acid has $\delta = 1·625$. Traube[6] finds that the cis-isomer has a smaller molecular volume than the trans-compound.

As a general rule, both isomers are colourless, but when it happens that one form shows a yellow tinge it is usually the one with the lower melting-point which is thus distinguished.

A short account of the difference in electrical conductivity produced by stereoisomerism will be found in Lehfeldt's *Electro-chemistry*, part i. It need only be said that in the case of monobasic stereoisomeric acids the isomer with the

[1] Vaubel, *J. pr. Chem.*, [2] **51**, 444 (1895) ; **59**, 30 (1899).

[2] Lassaigne, *Ann. Chim. Phys.*, [2] **11**, 93 (1819) ; Carius, *Annalen*, **142**, 153 (1867).

[3] Michael and Pendleton, *J. pr. Chem.*, **40**, 66 (1889).

[4] Baup, *Annalen*, **81**, 97 (1852).

[5] Kanatar and Tchelebijeff, *J. Russ. Phys. Chem. Soc.*, **22**, 549 (1890).

[6] Traube, *Annalen*, **290**, 43 (1896).

lower melting-point is usually the stronger, while in the dibasic acids the cis-form is stronger than the trans-form.

Name of stronger acid.	M.P.	K	Name of weaker acid.	M.P.	K
Isocrotonic acid . . .	15·5°	0·0036	Crotonic acid . . .	72°	0·0020
Angelic acid . . .	45°	0·0050	Tiglic acid	64·5°	0·0009
Maleic acid . . .	130°	1·17	Fumaric acid . .	—	0·093
Citraconic acid . . .	91°	0·340	Mesaconic acid . .	202°	0·079

Reference may be made to the work of Wegscheider,[1] Ostwald,[2] and Walden.[3]

As far as experimental work has gone, it has been found that the isomer with the highest melting-point, usually the trans-form, has the smaller heat of combustion. For example, we may give the following figures:[4]—

Maleic . .	326·900 cal.	Fumaric . .	319·278 cal.
Citraconic .	483·522 cal.	Mesaconic . .	479·060 cal.

Further instances are given in the papers of Stohmann.[5]

The heats of solution and neutralisation were measured by Gal and Werner,[6] in the cases of fumaric, maleic, mesaconic, and citraconic acids.

Name.	Heat of solution.	Heat of neutralisation.
Fumaric acid	−5,901 cal.	26,597 cal.
Maleic acid	−4,438 ,,	26,620 ,,
Mesaconic acid	−5,493 ,,	27,267 ,,
Citraconic acid .	−2,793 ,,	27,023 ,,

[1] Wegscheider, *Monatsh.*, **23**, 599 (1902).
[2] Ostwald, *Zeit. physikal. Chem.*, **3**, 380 (1889).
[3] Walden, *Zeit. physikal. Chem.*, **8**, 495 (1891).
[4] Louguinine, *Ann. Chim. Phys.*, [6] **23**, 186 (1891); Stohmann, *Zeit physikal. Chem.*, **10**, 416 (1892).
[5] Stohmann, *Ber.*, **28**, 134 (1895); *Zeit. physikal. Chem.*, **10**, 416 (1892)
[6] Gal and E Werner, *Bull. Soc. chim.*, **47**, 158 (1887).

Sir W. H. Perkin [1] finds that there is a difference between the values for the magnetic rotations of two stereoisomeric substances.

Very little work appears to have been done on the absorption spectra of ethylene stereoisomers.[2] Stewart [3] has found that in some cases the fumaroid form has a greater general absorption than the maleinoid type.

2. Chemical Properties.—A certain number of differences shown in the chemical properties of stereoisomers have already been dealt with in the sections on configuration determination; there is therefore no necessity to recapitulate them here.

Differences between the cis- and trans-forms of unsaturated acids are to be found in the amount of water of crystallization retained by certain of their salts. For example, the barium salt of maleic acid crystallizes with one molecule of water, while barium fumarate has three molecules of water of crystallization. The calcium and barium salts of isocrotonic acid have each three molecules of water of crystallization, while the corresponding salts of crotonic acid have none.

§ VI. *TRANSMUTATION.*

In considering the stereoisomers (1) and (2):—

$$\begin{array}{ccc} a\text{—C—}b & \qquad & a\text{—C—}b \\ \| & & \| \\ c\text{—C—}d & & d\text{—C—}c \\ (1) & & (2) \end{array}$$

it is obvious that the relative stability of the two compounds depends upon the relative strengths of the attractions between the groups *a*, *b*, *c*, and *d*. That is to say, if the attractions of *a* for *c* and *b* for *d* are together greater than the combined

[1] Perkin, senior, *Zeit. physikal. Chem.*, **21**, 641 (1896).

[2] Magini, *Atti R. Accad. Lincei*, **12**, II., 87, 260, 356 (1903); *J. Chim. phys.*, **2**, 410 (1904).

[3] Stewart, *Trans.*, **91**, 199 (1907).

attractions of *a* for *d* and *b* for *c*, then the configuration (1) will be the more stable of the two, since in it the attractive forces are most effectively employed. It is also evident that if the stability of (2) be disturbed in any way, instead of returning to its original configuration, it will more probably come to equilibrium in configuration (1). Further, the less stable isomer must have a greater energy content than the stable one —a conclusion which is confirmed by a comparison of the heats of combustion, for instance, of maleic and fumaric acids.

A disturbance of the stability of the labile isomer may be brought about in various ways, but nearly all cases may be classed under one or other of two heads—disturbance by physical influences, or disturbance by chemical influences. The change from the unstable to the stable configuration is called a *transmutation* of the one isomer into the other; and, contrary to the usual course of chemical reactions, it is generally not appreciably reversible; as soon as the labile isomer has been converted into the stable one, it remains without further change. This series of phenomena must now be described, and will be dealt with under the following heads:—

1. Transmutation by physical influence.
2. Transmutation by chemical influence.
3. Transmutation through intermediate ethane compounds.

1. Transmutation by Physical Influence.—Practically all labile isomers can be changed to the more stable form by raising the temperature to a certain extent, which is different for each substance. When maleic acid is raised to a few degrees above its melting-point, crystals of fumaric acid separate from the liquid.[1] The oily form of chlorostilbene is converted on distillation into the solid isomer.[2] In the cases where the stability of the two isomers is almost equal, heat produces from either a mixture of the two compounds as an end-product. Since this end-point is reached more rapidly from

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[1] Pelouze, *Annalen*, **11**, 266 (1834); Skraup, *Monatsh.*, **12**, 117 (1891); Tanatar, *Annalen*, **273**, 32 (1893).

[2] Sudborough, *Ber.*, **25**, 2237 (1892).

the labile isomer than from the stable variety, it serves in some cases to determine the relative stability of the two compounds. For example, from an estimation of the velocity with which the state of equilibrium is attained from each isomer, it was found possible to determine the relative stabilities of the α- and β-chloro crotonic acids. Sometimes the maleinoid can be obtained from the fumaroid form; *e.g.* phenoxy-fumaric by distillation[1] *in vacuo* gives phenoxy-maleic acid.

In some cases a more or less prolonged exposure to sunlight is sufficient to cause a transmutation of the isomers; and occasionally the effects of light are the reverse of those of heat; *e.g.* when the α-form of benzyl-β-amido-crotonic ester (M.P. 79°–80° C.) is heated, it is converted into the β-form (M.P. 21° C.), from which it can be regenerated by the action of light.[2] The work of Ciamician and Silber[3] and that of Paal and Schulze[4] may be consulted.

It has been observed that when some compounds are dissolved in a liquid which is afterwards evaporated, crystals of the other isomer are produced. Examples of this are found in the preparation of β-methyl-cinnamic acid by crystallizing the α-isomer,[5] and β-dibenzyl-ketone-benzylidene-*p*-toluidine by crystallizing the α-form from benzene containing a trace of phenylhydrazine.[6]

Spontaneous transmutation has been observed in a very limited number of cases.

2. Transmutation by Chemical Influence.—When maleic acid is heated in a sealed tube with water to about 130°, it yields fumaric acid.[7] It is not certain, however, that this change is due to the water, as the rise in temperature alone might be sufficient.

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[1] Ruhemann and Stapleton, *Trans.*, **77**, 1184 (1900).
[2] Mohlau, *Ber.*, **27**, 3376 (1894).
[3] Ciamician and Silber, *Ber.*, **36**, 4266 (1903).
[4] Paal and Schulze, *Ber.*, **35**, 168 (1902).
[5] Dain, *J. Russ. Phys. Chem. Soc.*, **29**, 32 (1897).
[6] Francis, *Trans.*, **81**, 441 (1902).
[7] Semenoff, *Bull. Soc. chim.*, **46**, 816 (1886); Skraup, *Monatsh.*, **12**, 107 (1891); Tanatar, *Annalen*, **273**, 32 (1893).

Halogen acids appear to be among the most active transmuting agents. In most cases it is sufficient to allow the acid and unsaturated compound to stand together for a time. Sunlight hastens the action; so also does heat. In the transmutation of the higher compounds of the acrylic acid series, nitrous acid has been found the most valuable reagent. In a few cases nitric acid has been employed. Sulphuric acid appears rather to retard than hasten the change from one isomer to the other.[1]

Of the halogens, chlorine and bromine are probably the most powerful transmuting agents known, a mere trace of the latter being sufficient to produce a change. Iodine is not very active. In their case also sunlight greatly increases the speed of transmutation.

Bases can be utilised only in a few cases; and as heat is required, it is doubtful whether the change is really due to the bases or not. It seems probable that the presence of the base merely prevents anhydride formation.

A few cases are known in which the process of saponification is sufficient to bring about transmutation. Maleic ester itself is not changed to fumaric acid by boiling with caustic potash, but its methyl derivative, citraconic acid, is transmuted in these circumstances into mesaconic acid. The reaction is reversible, however, for equilibrium is established when 70 per cent. mesaconic acid and 30 per cent. citraconic are present.[2] Maleinaminic acid is converted into maleic acid by boiling with aqueous potash; with alcoholic potash, fumaric acid is formed.[3]

In some cases a catalytic process may be employed for the purpose of transmuting one isomer into the other. At ordinary temperatures, sulphuretted hydrogen has practically no action upon a solution of maleic acid; but if certain salts of maleic acid, such as the copper salt, are decomposed by means of sulphuretted hydrogen, a considerable quantity of fumaric acid

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[1] Skraup, *Monatsh.*, **12**, 107 (1891).

[2] Delisle, *Annalen*, **269**, 95 (1892); Michael, *J. pr. Chem.*, [2] **46**, 209 (1892).

[3] Anschutz, *Annalen*, **273**, 32 (1893).

is formed. Silver maleate also, when acted on by sulphuretted hydrogen, yields some fumaric acid, though, if it be treated with hydrochloric acid, only maleic acid is produced. Again, when a solution of maleic acid is saturated with sulphur dioxide and sulphuretted hydrogen, and then warmed so that a reaction occurs between the two gases, fumaric acid is produced; though no such result follows the solution of maleic acid in water which contains either a mixture of, or the end-products of the reaction between, sulphuretted hydrogen and sulphur dioxide. Since, under ordinary conditions, sulphur dioxide is practically without action upon maleic acid, it must be concluded that the change from maleic to fumaric acid has in this instance been brought about by some influence which is produced by the action between the two gases.[1]

A few other instances of changes brought about by chemical agents may be mentioned. When concentrated solutions of maleic acid and potassium sulphocyanide are mixed, fumaric acid is formed. A small quantity of sulphuretted hydrogen is evolved from the mixture.[2] Maleic acid is converted into fumaric acid by the gases evolved by the action of nitric acid upon arsenious acid.[3] Sulphur dioxide, under certain special conditions, has the same property of causing transmutation.[4]

3. Transmutation through Intermediate Ethane Compounds.—This case has already been mentioned. The method consists in adding on certain radicals to the double bond, and then splitting off other radicals, thus inducing a change in configuration as well as in constitution. In general, the course of the reactions may be represented as follows:—

$$\begin{array}{c} a\text{—}C\text{—}b \\ \| \\ a\text{—}C\text{—}b \end{array} + \begin{array}{c} d \\ | \\ d \end{array} = \begin{array}{c} d \\ | \\ a\text{—}C\text{—}b \\ | \\ a\text{—}C\text{—}b \\ | \\ d \end{array} \xrightarrow{\text{Revolution}} \begin{array}{c} d \\ | \\ a\text{—}C\text{—}b \\ | \\ d\text{—}C\text{—}a \\ | \\ b \end{array} - bd = \begin{array}{c} a\text{—}C\text{—}b \\ \| \\ d\text{—}C\text{—}a \end{array}$$

[1] Skraup, *Monatsh.*, **12**, 107 (1891).
[2] Michael, *J. pr. Chem.*, [2] **52**, 324 (1895).
[3] Schmidt, *Ber.*, **33**, 3241 (1900).
[4] Franz, *Monatsh.*, **15**, 209 (1894).

In this manner maleic acid may be converted into bromo-fumaric through dibromo-succinic, while fumaric acid can be changed into bromo-maleic acid.

§ VII. *EXPLANATIONS OF THE TRANSMUTATION OF ETHYLENE ISOMERS.*

1. **Wislicenus's Explanation.** — (*a*) *Transmutations by Physical Influences.*—"These processes are to be traced to an intramolecular rearrangement, brought about by the lessening of binding energy which is caused by the action of heat. Thus either an interchange of position occurs between the radicals united with the C : C group in order to produce a more stable compound, or the double bond between the carbon atoms is loosened so far, that by the action of strong affinities a turning

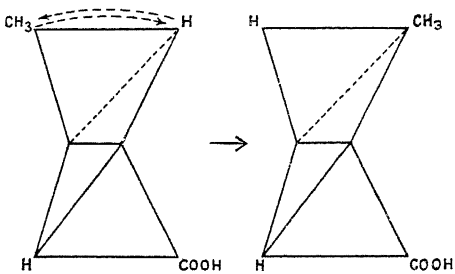

FIG. 34.

movement of the system follows, after which comes a wandering of a hydrogen atom to the nascent affinity of one of the radicals not causing this rotation, and finally, the re-formation of the double bond takes place."[1] Figure 35 shows the process of transmutation of isocrotonic into crotonic acid on the Wislicenus hypothesis.

(*b*) *Transmutations by Chemical Influences.*—He explains all these by a process of addition to form ethane compounds, and

[1] Wislicenus, *Raumliche Anordnung*, p. 55.

a subsequent loss of the added radicals after rotation has taken place. For example, in the case of the conversion of

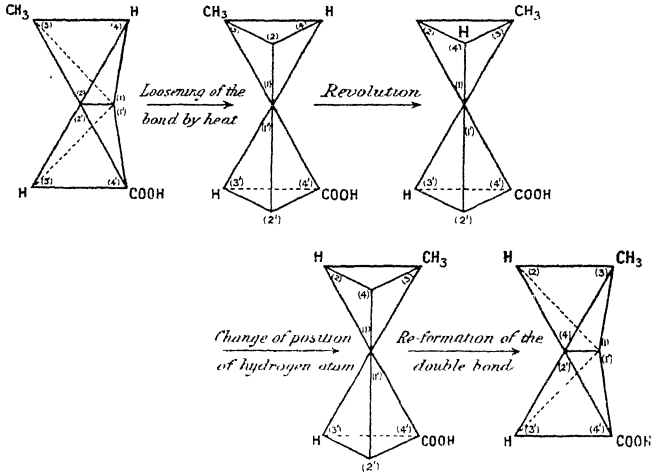

FIG. 35.

maleic to fumaric acid, he supposes the following changes to occur:—

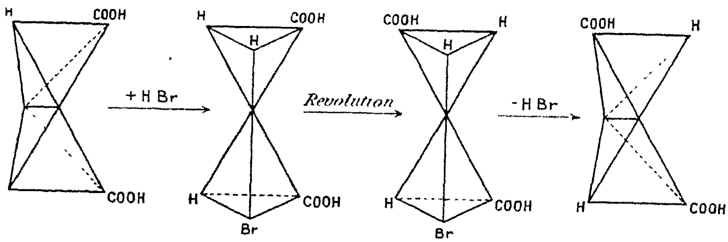

FIG. 36.

This explanation has been proved to be entirely inadequate. To go no further, it need only be pointed out that in the case of methyl-citraconic acid:[1]—

[1] Fittig, *Ber.*, **29**, 1842 (1896).

$$\begin{array}{c} CH_3.C.COOH \\ \| \\ CH_3.C.COOH \end{array}$$

there is no possibility of the exchange of hydrogen atoms such as is shown in the above case, and without such an exchange the explanation falls to the ground. Even if this objection could be answered, however, the work of Anschutz, Fittig, Skraup, and Michael has shown that, in the conditions of the transmutation of one isomer into another, the intermediate compounds postulated by Wislicenus are stable, and so cannot be supposed to break down into unsaturated bodies.

(*c*) *Transmutation through Ethane Compounds.*—In his explanation of this, Wislicenus assumes an addition of two atoms of bromine in the cis-position and a subsequent elimination of hydrobromic acid, also from the cis-position. The following facts will show that this is unfounded. Lossen and Riebensahm[1] found that when iso-dibromo-succinic acid obtained from maleic acid was made to react with water, 80 per cent. of the reaction-product was racemic acid, and the remaining 20 per cent. was meso-tartaric acid. This is just the reverse of what might be expected if iso-dibromo-succinic acid were a cis-addition-product of maleic acid. Again, fumaric acid with bromine yields a dibromo-succinic acid which on treatment with water gives about 80 per cent. of meso-tartaric, and only about 20 per cent. of racemic acid. It is thus clear that oxidation and the addition of bromine lead to very different types of compound.

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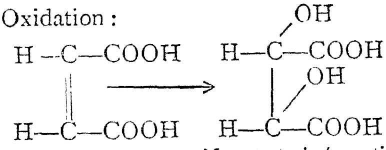
[1] Lossen and Riebensahm, *Annalen*, **292**, 295 (1897).

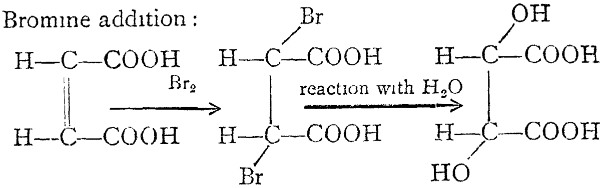
Maleic acid :—

Oxidation :



Meso-tartaric (quantitative).

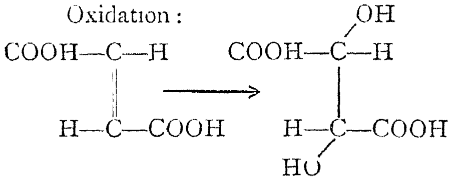
Bromine addition :



Isodibromo-succinic. Racemic (80 %).

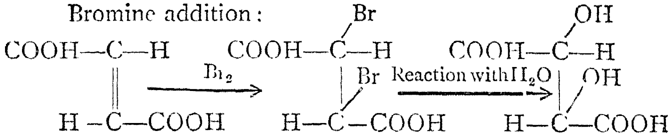
Fumaric acid :—

Oxidation :



Racemic (quantitative).

Bromine addition :



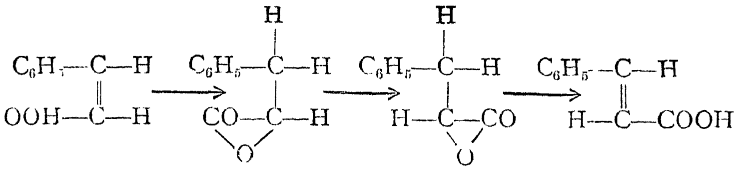
Dibromo-succinic. Meso-tartaric (80 %).

From the above it is evident that in the case of maleic acid oxidation gives cis-addition-products, while halogen addition yields trans-derivatives. On the other hand, fumaric acid when oxidised produces trans-addition-products, and adds on halogens in the cis-position.

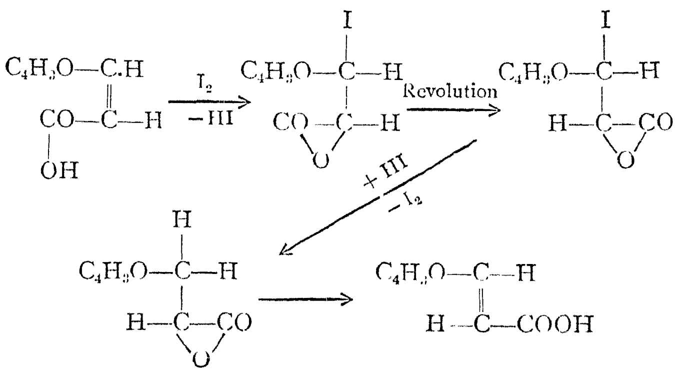
2. Liebermann's Explanation.[1]—To explain the change of

[1] Liebermann, *Ber.*, 23, 2513 (1890).

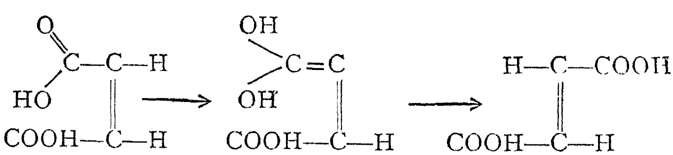
isocinnamic into cinnamic acid under the action of heat or light, he proposed the following series of reactions :—



While with iodine the result would be as follows in the case of allo-furfur-acrylic acid :[1]—



A variation of this is found in the explanation offered by tautomerism, where the unstable enolic form (produced by a wandering of the ethylene hydrogen atom to the carbonyl of the carboxyl group) is supposed to be the intermediate product :—



[1] Liebermann, *Ber.*, **28**, 1444 (1895)

3. Skraup's Explanation.—Skraup,[1] in his researches upon the transmutation of the unsaturated acids, found that the ethane derivatives considered by Wislicenus to be intermediate compounds, were actually formed during the course of transmutation, but that they could not be real intermediate compounds, as they were stable under the conditions of the experiment; nevertheless, the fact that such compounds were always formed, even if in very small quantity, suggested to Skraup that there might be some connection between their formation and the transmutation which occurred simultaneously. In his view, the one reaction had a catalytic action upon the other; or, to use his own analogy, the addition reaction set up in the ether certain waves which acted upon the second reaction just as sound-waves act upon a string tuned to their note. He was able to prove also that this catalytic action was found in the case of both endothermic and exothermic reactions. Further, he showed that the action of sulphuretted hydrogen upon the maleates of the heavy metals was sufficient to convert some of the maleic acid into fumaric; and that the amount of maleic acid thus transformed varied according to the metal chosen. For example:—

Salt	Per cent. of fumaric formed.
Copper . .	13·7
Lead . .	16·2
Nickel . .	1·9
Cadmium . .	19·8
Zinc . .	1·8

4. Werner's Explanation.—This hypothesis is based upon the idea of the double bond put forward by Werner,* in which he supposes that only a very small fraction of the total affinity which makes up the double bond is employed in preventing the free rotation of the carbon atoms about their

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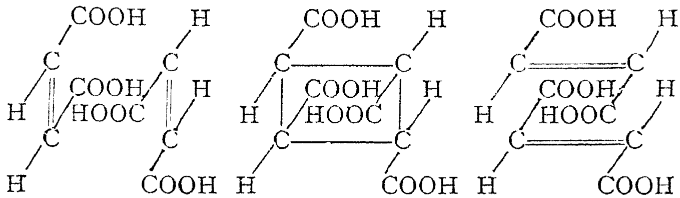
* See p. 161.

[1] Skraup, *Monatsh.*, **12**, 146 (1891).

axis of union. Werner assumes that an increase of temperature or other influences would be sufficient to overcome this slight resistance, and so cause the atoms to group themselves in the more stable position.

5. **Stewart's Explanation.**[1]—In this explanation, the formation and disruption of a tetramethylene compound by intermolecular collisions is assumed. In the case of the conversion of maleic into fumaric acid by means of heat, the intermediate compound would be a tetramethylene-1,2,3,4-tetra-carboxylic acid, in which, probably, the carboxyl groups attached to the 1,2-carbon atoms would lie on the side of the ring opposite to those attached to the 3,4-atoms. Such a tetramethylene ring might split apart in two ways: either by breaking the linkings between the carbon atoms 1 and 2, 3 and 4; or by breaking those joining 1 to 4 and 2 to 3. In the former case, fumaric acid is formed; in the latter, maleic acid is regenerated. If, however, fumaric acid is produced, owing to its higher melting-point, it is immediately withdrawn from further action, while maleic acid is free to undergo the same series of changes.

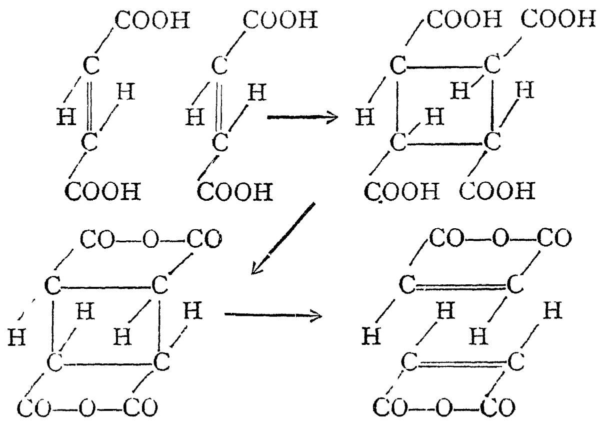


Maleic acid. Tetramethylene-1, 2, 3, 4-tetra-carboxylic acid. Fumaric acid.

Fumaric acid, when distilled in presence of phosphorus pentoxide, is assumed to form the same type of tetramethylene derivative; but in this case water is abstracted from the carboxyl groups attached to the 1,2 carbon atoms, and also from those attached to the 3,4 atoms, the groups in each pair being in the cis-position to one another. Owing to the presence of the two anhydride chains, the tetramethylene ring

[1] Stewart, *Proc.*, **21**, 73 (1905).

cannot now break across in either of two ways, as in the last case, but only in the manner shown below; and consequently its disruption produces maleic anhydride:—



The formation of fumaryl chloride from maleic anhydride by means of pentachloride of phosphorus, and its regeneration by treating the fumaryl chloride with silver fumarate, can also be explained on the above hypothesis, so that the complete series of changes shown below can be made clear:—

↗ Fumaric acid ↘

Maleic acid ← Maleic anhydride

Fumaryl chloride ↙↗

That the formation of such an intermediate compound is possible is proved by the fact that in some cases it has been found that ethylene compounds do polymerise in this way: *e.g.* cinnamic acid produces truxillic acid,[1] stilbene gives distilbene,[2] cyclopentadiene yields a bimolecular compound,[3]

[1] Riiber, *Ber.*, **35**, 2908 (1902); Ciamician and Silber, *Ber.*, **35**, 4129 (1902).

[2] Ciamician and Silber, *Ber.*, **35**, 4129 (1902).

[3] Kraemer and Spilken, *Ber.*, **29**, 558 (1896).

cinnamylidene-malonic acid gives diphenylene-tetramethylene-bismethylene-malonic acid,[1] and all these break down on distillation into two molecules of the original compound. The objection has been made that if the tetramethylene ring were actually formed, it would be too stable to break down spontaneously. This may be met by supposing that the ring is not actually formed, but that, instead, a mere collision of two molecules occurs, and that this collision so disturbs the internal equilibrium that when the molecules separate they split apart in such a way as to form two others of a more stable type.

§ VIII. *PFEIFFER'S THEORY.*

Owing to the inadequate way in which the van't Hoff-Le Bel hypothesis answers the demands made upon it by the work of Michael, another theory[2] has come into the field, which seeks to overcome the difficulty.

Pfeiffer, in the first place, puts aside the question as to the direction in which valency acts in space; and consequently gives up the van't Hoff-Le Bel hypothesis entirely. He supposes that in a compound of the type $a_3C.Ca_3$ the groups a are arranged at the corners of an octahedron whose centre is occupied by the complex C : C, as to whose character he makes no assumptions.

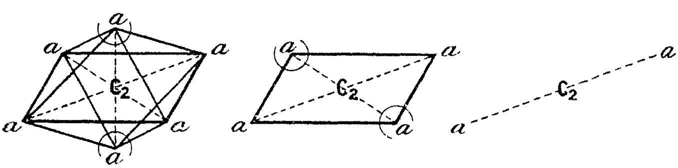


FIG. 37.

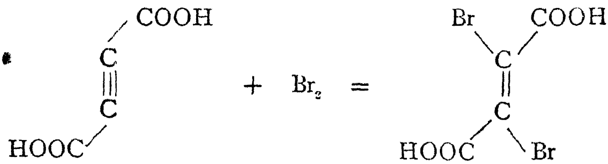
In order to pass from the ethane series to the olefines, two a groups must be removed from the molecule. To do this

[1] Riiber, *Ber.*, **35**, 2908 (1902).
[2] Pfeiffer, *Zeit. physikal. Chem.*, **48**, 40 (1904).

in the most symmetrical manner, those groups marked with a circle are taken away, and the result is the plane figure. Conversion of this olefine compound into an acetylene derivative is similarly brought about, and again the most symmetrical way of removing the groups is to take those marked with circles in the plane figure.

It will be seen that there is a certain similarity between such space formulæ and those suggested by Werner for the cobalt and platinum compounds, which will be dealt with later in this volume.*

If we now consider the reverse process, *i.e.* addition, we shall find that the new atoms must be added on in the trans-position to one another. For instance, the addition of bromine to acetylene dicarboxylic acid may be expressed as follows :—



The addition of bromine to maleic and fumaric acids takes place, on this theory, in the trans-position, which is in agreement with experimental evidence :—

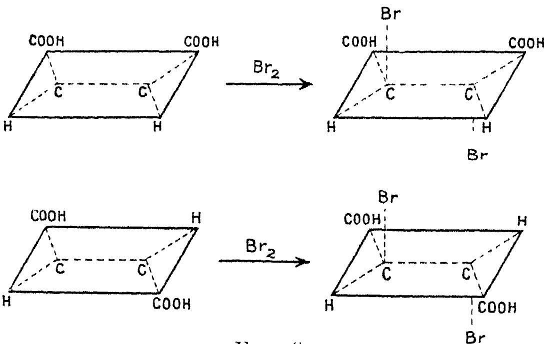


FIG. 38.

* See Chapter V. of this part.

This theory, then, accounts for the main facts of halogen addition to the unsaturated compounds. The question of the oxidation of these bodies is, however, not quite so easy to explain, as here addition takes place in the cis-position. Pfeiffer postulates that in this case an oxide is first formed, which forms a bridge, then adds on water to produce the hydroxy-compound as shown in Fig. 39 :—

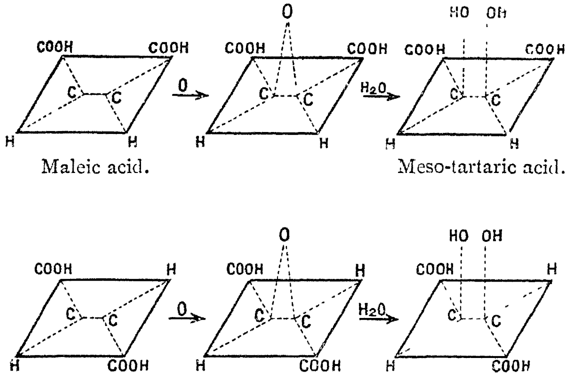


FIG. 39.

This explanation is just as good as the van't Hoff-Le Bel one, and no better. It would seem that a complete explanation of these phenomena is still to be found; and in all probability it will be derived from a fusion of both the van't Hoff and the Pfeiffer theories.

Bruni[1] points out that the conclusions arrived at by Pfeiffer are in agreement with the results obtained by himself and his collaborators from a study of solid solutions. He gives the following table. The numbers in brackets give the melting-points of the substances :—

[1] Bruni, *Atti R. Accad. Lincei*, [5] **13**, I. 626 (1904).

Saturated compounds.	Compounds not forming solid solutions with saturated compounds.	Compounds forming solid solutions with saturated compounds.	
	Ethylenic compounds.	Ethylenic compounds.	Acetylenic compounds.
Dimethyl succinate (19° C.)	Dimethyl maleate (liquid)	Dimethyl fumarate (102° C.)	Dimethyl acetylene dicarboxylate
Butyric acid (4° C.)	Isocrotonic acid (liquid)	Crotonic acid (72° C.)	—
Phenyl-propionic acid (48° C.)	Allocinnamic acid (69° C.)	Cinnamic acid (133° C.)	Phenyl-propiolic acid
Dibenzyl (52° C.)	Isostilbene (liquid)	Stilbene (124° C.)	Tolane
Dimethyldibenzyl (82° C.)	—	*pp*-Dimethyl-stilbene (177° C.)	—

From these results Bruni draws the conclusion that all the compounds in the third column of the table have the fumaroid configuration, which agrees with what is known of their other physical and chemical properties; while the compounds in the second column are maleinoid in character. The acetylene acid saturated compounds range themselves together with the fumaroid derivatives, and it is probable that they have analogous configurations.

§ IX. *COMPOUNDS WITH TWO DOUBLE BONDS*

In the case of compounds which contain two double bonds, such isomers as the following may exist:—

$$ab.\mathrm{C}:\mathrm{CR.CR'}:\mathrm{C}ab, \quad ab.\mathrm{C}:\mathrm{CR.CR'}:\mathrm{C}bc, \quad ab.\mathrm{C}:\mathrm{CR.CR'}:\mathrm{C}.cd$$

Of these it is only necessary to give one example in full, as the others can easily be worked out on the same principle:—

$$\begin{array}{cc} \mathrm{R.C} & \!\!—\!\!—\mathrm{C.R'} \\ \| & \| \\ b.\mathrm{C}.a & a.\mathrm{C}.b \end{array} \qquad \begin{array}{cc} \mathrm{R.C} & \!\!—\!\!—\mathrm{C.R'} \\ \| & \| \\ a.\mathrm{C}.b & b.\mathrm{C}.a \end{array} \qquad \begin{array}{cc} \mathrm{R.C} & \!\!—\!\!—\mathrm{C.R'} \\ \| & \| \\ a.\mathrm{C}.b & a.\mathrm{C}.b \end{array} \qquad \begin{array}{cc} \mathrm{R.C} & \!\!—\!\!—\mathrm{C.R'} \\ \| & \| \\ b.\mathrm{C}.a & b.\mathrm{C}.a \end{array}$$

§ X. *SOME UNEXPLAINED CASES OF ISOMERISM IN THE ETHYLENE SERIES.*

The most generally quoted case is that of the three varieties of cinnamic acid. According to the commonly accepted ideas, this compound should exist in two stereoisomeric forms; but actually three are known. The three acids are sharply distinguished from one another, both in their own physical properties and in those of their salts. Allo-cinnamic is more stable than is usually the case with labile isomers, as it can be repeatedly melted without any considerable amount being converted into the ordinary acid. Common cinnamic in all its physical properties behaves as if it were the fumaroid form of allo-cinnamic; but in chemical properties the conditions are reversed; allo-cinnamic appears to be fumaroid as far as chemical actions are concerned.[1] Another peculiar feature of these acids is that their dibromides all yield the same bromstyrol. Erlenmeyer junior[2] has proposed the following formulæ to explain the extra isomer:—

$$\begin{array}{c} C_6H_5{-}C{-}H \\ \| \\ COOH{-}C{-}H \end{array} \qquad \begin{array}{c} C_6H_5{-}C{-}H \\ \| \\ H{-}C{-}COOH \end{array} \qquad \begin{array}{c} / \\ C_6H_5{-}C{-}H \\ | \\ COOH{-}C{-}H \\ / \end{array} \qquad \begin{array}{c} C_6H_5{-}C{-}H \\ /\,|\,/ \\ COOH{-}C{-}H \end{array}$$

The figures with free valencies are intended to represent iso-cinnamic acid.

Another exception to the ordinary ideas is to be found in the two dibenzoyl-acetones discovered by Claisen.[3] He rejects as inadequate the explanation offered by the two formulæ:—

$$\begin{array}{c} C_6H_5{-}C{-}OH \\ \| \\ CH_3CO{-}C{-}CO{-}C_6H_5 \end{array} \qquad \begin{array}{c} C_6H_5{-}C{-}OH \\ \| \\ C_6H_5{-}CO{-}C{-}CO{-}CH_3 \end{array}$$

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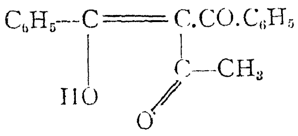
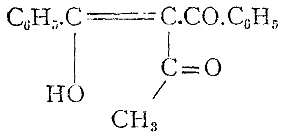
[1] Michael, *Ber.*, **34**, 3640 (1901).

[2] Erlenmeyer junior, *Annalen*, **287**, 1 (1895); *Ber.*, **36**, 2340 (1903).

[3] Claisen, *Annalen*, 277, 191 (1893).

and prefers the following, where the differences in chemical properties are explained by the different positions of the hydroxyl and carbonyl groups :—





CHAPTER III.

GEOMETRICAL ISOMERISM IN CARBON-NITROGEN COMPOUNDS.

§ I. *HISTORICAL.*

In 1883 Victor Meyer and Goldschmidt[1] prepared a dioxime of benzil; and later in the same year Goldschmidt[2] synthesised a second benzil dioxime. The existence of this second isomer could not be explained by any theory then current, and in order to clear up the matter, V. Meyer and Auwers[3] investigated the properties of the two compounds. They found that instead of two there were in reality three isomers, all of which possessed the same structural formula :—

$$\begin{array}{l} C_6H_5.C : N.OH \\ \quad\quad\; | \\ C_6H_5.C : N.OH \end{array}$$

To explain this, they assumed that the free rotation of two singly bound carbon atoms about their common axis may in certain cases be hindered; and that in the case of the benzil dioximes there are three stable positions which the atom groups may take up. If, for the sake of clearness, we represent the group $=N.OH$ by the two letters *n—n*, the following formulæ represent these three stable positions :—

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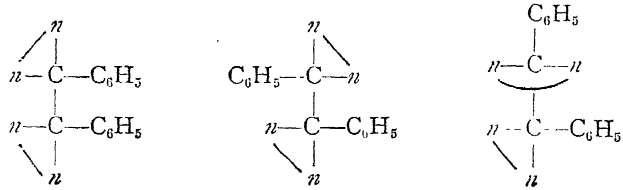
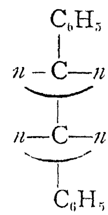
[1] V. Meyer and Goldschmidt, *Ber.*, **16**, 1616 (1883).

[2] Goldschmidt, *ibid.*, **16**, 2176 (1883).

[3] V. Meyer and Auwers, *ibid.*, **21**, 784, 815, 3510 (1888) ; **22**, 537, 564, 705, 1985, 1996 (1889).



To these they were obliged[1] to add a fourth :—



and for the monoxime of benzil three similar formulæ were proposed.

If these conceptions held good, however, there should be four structurally identical isomers of benzil monoxime and of benzil itself; but up to the present only two such isomers of the monoxime have been found, while no isomeride having the same structure as benzil is known.

The researches of Beckmann[2] now called attention to the isomerism of the benzaldoximes. It was shown by Goldschmidt[3] that the two isomeric benzaldoximes which Beckmann had discovered were not, as had been supposed, structural isomers, but were structurally identical, and he added, "Perhaps we are now dealing with a kind of stereoisomerism which cannot be explained in terms of the current hypotheses." The work of Goldschmidt showed the untenability of the Meyer-Auwers hypothesis, since by means of it no explanation could be given which accounted for the known facts. The difficulty of explaining why the isomerism was present in the

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[1] V. Meyer and Auwers, *Ber.*, **23**, 594 (1890).
[2] Beckmann, *ibid.*, **20**, 2766 (1887) ; **22**, 429, 1531 (1889).
[3] Goldschmidt, *ibid.*, **22**, 3112 (1889).

case of the derivatives of carbonyl compounds and yet not present in the case of the root-compounds themselves, was not surmounted until 1890, when Hantzsch and Werner published their paper *On the Space Arrangement of Atoms in Molecules containing Nitrogen.*[1]

§ II. *THE GENERAL CHARACTER OF THE STEREO-ISOMERIC CARBON-NITROGEN COMPOUNDS.*

1. **The Necessary Structural Conditions.**—It has been found that in all cases where stereoisomerism is observed in the case of carbon-nitrogen compounds, a double bond is present between the carbon and nitrogen atoms; and further, that when this double bond is eliminated by reduction the compound loses its property of appearing in two forms. For example, though there are two benzaldoximes known, there is only one benzyl-hydroxylamine:—

$$\begin{array}{c} C_6H_5\text{—}C\text{—}H \\ \| \\ N.OH \end{array} \qquad\qquad \begin{array}{c} C_6H_5\text{—}CH_2 \\ | \\ NH.OH \end{array}$$

Two isomers known. Exists in one form only.

The double bond alone, however, is not sufficient to produce isomerism, for benzophenone oxime exists in only one form. It has been ascertained that in order that a compound may show this type of stereoisomerism it must contain two dissimilar radicals attached to the carbon atom, which is doubly linked to the nitrogen atom:—

$$\begin{array}{c} C_6H_5\text{—}C\text{—}C_6H_5 \\ \| \\ N.OH \end{array} \qquad\qquad \begin{array}{c} C_6H_5\text{—}C\text{—}C_6H_4.CH_3 \\ \| \\ N.OH \end{array}$$

Only one isomer known. Two isomers known.

It is therefore possible to express in a general formula the

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[1] Hantzsch and Werner, *Ber.*, **23**, 11 (1890).

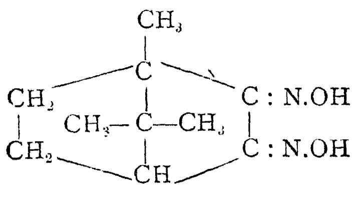
structural conditions which must be fulfilled in order to render possible the appearance of stereoisomerism in these compounds :—

$$\begin{array}{c} R—C—R' \\ \| \\ N \\ | \\ a \end{array}$$

2. The Number of Isomers found.—If a compound contains only one double bond between a carbon and a nitrogen atom, two is the highest number of isomeric forms observed. If more than one such double bond be present in the molecule, the number of isomers may increase. The complexity of the molecule also exercises some effect upon the number of isomers found. Thus in the case of benzaldoxime, (I.), there are two isomers known; benzildioxime, (II.), which contains two double bonds, gives three isomers; and camphorquinone, being a very complicated tri-cyclic compound, gives no less than four isomeric dioximes (III.).

$$\text{(I.)} \quad C_6H_5.CH : N.OH$$

$$\text{(II.)} \quad \begin{array}{l} C_6H_5—C : N.OH \\ \qquad\quad | \\ C_6H_5—C : N.OH \end{array}$$

(III.) 

3. The Structural Identity of the Isomers.—The exhaustive researches of Victor Meyer and Auwers, which the latter has described in his pamphlet *Die Entwicklung der Stereochemie*, proved conclusively that the isomerism with which we are now dealing could not be referred to any

difference in structure between the two isomers. It would occupy too much space to give even an outline of these researches, and it will suffice if we take one or two examples of the reasoning employed.

In the case of the benzaldoximes, two forms are known. Both of these are easily split up by acids into hydroxylamine and the original aldehyde. Leaving for the moment the question of the benzene nucleus, there are three possible forms which could correspond to structural differences in the rest of the molecule :—

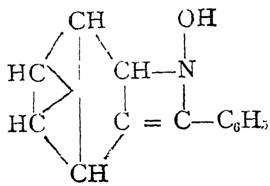
$$\begin{array}{ccc} C_6H_5\text{—}CH : N.OH & C_6H_5\text{—}\overset{\quad O}{\overset{\diagup\;|}{CH\text{—}NH}} & C_6H_5\text{—}CH_2\text{—}N : O \\ \text{(I.)} & \text{(II.)} & \text{(III.)} \end{array}$$

The formula (III.) is in disagreement with all the main properties of the substances, both of which are colourless, while a compound of the given type would probably be blue, like a nitroso-compound. Further, the substances dissolve easily in alkalis, and can be regained unaltered from the alkaline solution. It is therefore probable that if the isomerism were structural in character, it could best be expressed by the first two formulæ. Such an explanation, however, does not agree with the ease with which the derivatives of one form are converted into those of the other form. For instance, the acetyl derivative of one form of benzaldoxime goes over almost instantaneously into the other form when acted on by moist hydrochloric acid. The change is much more easily accomplished than is usual in the case of an alteration in structure; and it recalls rather the change of one ethylene isomer into another. A more convincing proof is to be found in the fact that certain alkyl derivatives of the aldoximes exist not only in two isomeric forms corresponding to the formula R.CH : N.OR′, but also in another form corresponding to the structure isomer :—

$$\underset{\underset{O}{\diagdown\;\diagup}}{R.CH\text{—}N\text{—}R'}$$

Now, obviously, if the only difference between the two oximes were a structural one, there would be only one alkyl derivative corresponding to each oxime.

Claus[1] has put forward the idea that the aromatic ketoximes exist in two forms, owing to a change in the benzene nuclei: one isomer being represented as :—



This formula, however, stands in contradiction to the whole character of the substances.

§ III. *HYPOTHESES AS TO THE MOLECULAR CONFIGURATION OF THE CARBON-NITROGEN ISOMERS.*

Since the cause of the isomerism which was observed in these compounds could not be a structural difference between them, the only remaining explanation was a stereochemical one. In the historical section, a brief account has been given of one attempt to explain the phenomena; and others of a similar character were put forward at various times.[2] The most probable of all was advanced by Hantzsch and Werner,[3] and as it explains practically all the known facts, it is generally accepted at the present day.

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[1] Claus, *J. pr. Chem.*, [2] **45**, 389 (1892); **54**, 391 (1896).

[2] Wilgerodt, *ibid.*, [2] **37**, 449 (1888); Burch and Marsh, *Trans.*, **55**, 656 (1889).

[3] Hantzsch and Werner, *Ber.*, **23**, 11 (1890).

Just as van't Hoff assumed that the four valencies of a carbon atom were tetrahedrally situated in space, Hantzsch and Werner put forward the hypothesis that the three valencies of nitrogen could not lie in a plane. Instead, they supposed that in certain compounds the third valency lay in a plane other than that which contained the first two; and they expressed their idea as follows :—

"*In certain compounds the three valencies of the nitrogen atom act toward the corners of a (not necessarily regular) tetrahedron, in whose fourth corner the nitrogen atom itself is situated.*"

By means of this hypothesis it is easy to draw a parallel between the cases of isomerism in the ethylene series and those which occur in the oximes and similar compounds. In the one case we have the structure (I.), and in the other (II.) :—

$$\text{(I.)}\quad \begin{array}{c}\mathrm{A{-}C{-}B}\\ \| \\ \mathrm{Y{-}C{-}Z}\end{array} \qquad\qquad \text{(II.)}\quad \begin{array}{c}\mathrm{A{-}C{-}B}\\ \| \\ \mathrm{N{-}Z}\end{array}$$

And since the ethylenic compounds can occur in two isomeric forms corresponding to the formulæ :—

$$\begin{array}{c}\mathrm{A{-}C{-}B}\\ \| \\ \mathrm{Y{-}C{-}Z}\end{array} \qquad\qquad \begin{array}{c}\mathrm{A{-}C{-}B}\\ \| \\ \mathrm{Z{-}C{-}Y}\end{array}$$

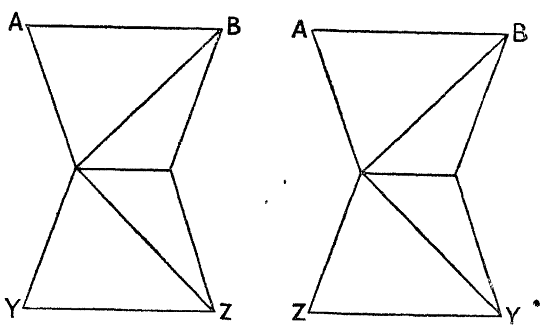


FIG. 40.

so we should expect that the nitrogen compounds also would occur in the forms :—

$$\begin{array}{c} A—C—B \\ \| \\ N—Z \end{array} \qquad\qquad \begin{array}{c} A—C—B \\ \;\;\| \\ Z—N \end{array}$$

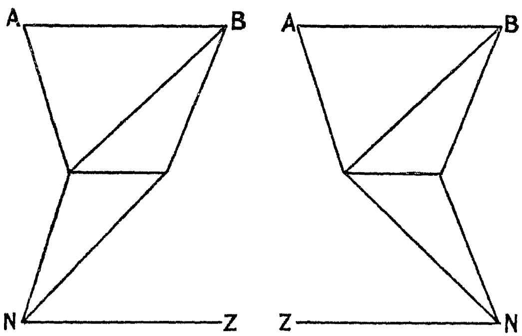


Fig. 41.

In recent years there has been a tendency to assume that certain symbols actually represent the whole of the true state of things in a molecule, and this literal interpretation of symbols apart from their implied limitations has had the effect of confusing the subject to a very considerable extent. It cannot be too strongly insisted that the grouping which Hantzsch and Werner assumed for the nitrogen valencies is to be considered as the *effect* of forces within the molecule; and must not be supposed to be *in itself* the cause of the isomerism. The real cause of the space position of the group attached to the nitrogen atom by a single bond must be sought in the attractions which the other groups in the molecule exert upon it. A crude representation of the matter may be given by assuming that the attraction is due to static electricity, in which case the figure below indicates the state of affairs. The pith-ball Z will tend to rise toward B rather than to approach A, and if the forces at work in the system be properly

balanced, it will remain in the position shown by the dotted lines :—

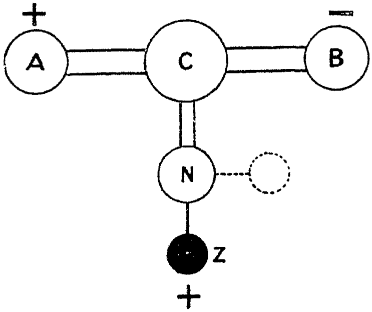


FIG. 42.

Now, in the case of a molecule such as :—

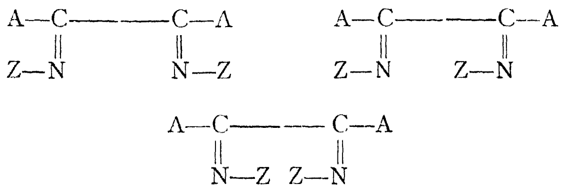
$$\begin{array}{c} X\text{—}C\text{—}Y \\ \Vert \\ N \\ | \\ Z \end{array}$$

in which Z is situated symmetrically with respect to X and Z, Y there will be certain forces at work between X and Z on the one side, and Y and Z on the other; and it is to be expected that if the forces are unequal Z will leave its central position and will tend to approach either X or Y. Should the attraction of X greatly exceed that of Y, the chance of Z taking up a stable position near Y would be very small: in such a case the compound would probably not occur in isomeric forms; and the existing compound would correspond to an unsymmetrical situation of Z. It is easy to see that in certain cases it might be possible for Z to assume a fairly stable situation near X or near Y. In this case two isomers would exist, one of which would be convertible into the other with great ease.

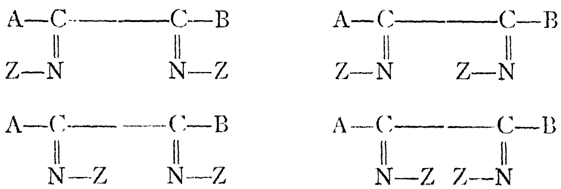
From what has already been said, the possible number of isomers for a given case can be deduced. For example, in the case of a compound which contains one double bond

between a carbon and a nitrogen atom, there should be two isomers :—

In the case where two such double bonds exist, the matter is more complicated, since here three isomers are possible when the compound is symmetrical :—



When the compound is unsymmetrical in structure, yet another isomer is possible, making four in all :—



§ IV. *THE CLASSIFICATION AND NOMENCLATURE OF THE STEREOISOMERIC CARBON-NITROGEN COMPOUNDS.*

There are six classes of the isomers which are explained by the Hantzsch-Werner hypothesis :—

1. Aldoximes.
2. Ketoximes (including dioximes).

3. Hydrazones (including osazones).

4. Anils.

5. Semicarbazones, thiosemicarbazones, and thiosemicarbazides.

6. Chlorimides and other unimportant compounds.

Of these the oximes and hydrazones are the most important.

The simplest case is that of the aldoximes, in which the nomenclature employed is as follows. If the hydroxyl group lies on the same side of the molecule as the hydrogen atom of the aldehyde, the compound is called a *syn-aldoxime;* while if the two lie on opposite sides of the molecule, it is termed an *anti-aldoxime.* For instance, in the case of benzaldoxime the two forms are :—

$$\begin{array}{c} C_6H_5—C—H \\ \quad\ \ \| \\ \qquad N—OH \end{array} \qquad\qquad \begin{array}{c} C_6H_5—C—H \\ \qquad\ \| \\ HO—N \quad \end{array}$$

Benzsynaldoxime. Benzantialdoxime.

In the case of the ketoximes a similar method is adopted. It will be made clearest by using a practical example. Phenyl-tolyl-ketoxime occurs in two forms, which are distinguished from one another by the use of the terms *syn-* and *anti-*, just as in the last case. Here, when the hydroxyl group is on the same side of the molecule as the phenyl radical, the substance is called "syn-phenyl-tolyl-ketoxime;" while if the phenyl and hydroxyl groups are on opposite sides of the molecule, the compound is termed "anti-phenyl-tolyl-ketoxime."

$$\begin{array}{l} C_6H_5—C—C_6H_4.CH_3 \\ \qquad\ \ \| \\ \ \ HO—N \end{array} \qquad\qquad \begin{array}{l} C_6H_5—C—C_6H_4.CH_3 \\ \qquad\quad \| \\ \qquad\ N—OH \end{array}$$

Syn-phenyl-tolyl-ketoxime. Anti-phenyl-tolyl-ketoxime.

When there are two oxime groups in the same compound, for example, in the case of benzil dioxime, another nomenclature is used. The prefix *syn-* is used when the two hydroxyl groups are in proximity to one another; the prefix *anti-* when they are turned away from one another; and the position intermediate between these two is called the *amphi-* position.

$$\begin{array}{ccc} C_6H_5\text{—}C & \text{———} & C\text{—}C_6H_5 \\ \| & & \| \\ NOH & & HON \end{array} \qquad \begin{array}{ccc} C_6H_5\text{—}C & \text{———} & C\text{—}C_6H_5 \\ \| & & \| \\ HON & & NOH \end{array}$$

Benzil-syn-dioxime. Benzil-anti-dioxime.

$$\begin{array}{ccc} C_6H_5\text{—}C & \text{———} & C\text{—}C_6H_5 \\ \| & & \| \\ NOH & & NOH \end{array}$$

Benzil-amphi-dioxime.

§ V. *THE DETERMINATION OF THE CONFIGURATION OF CARBON-NITROGEN STEREOISOMERS.*

In the case of the ethylene stereoisomers it was taken for granted that in intramolecular reactions, changes will occur most easily when the reacting atoms are situated near one another in the molecule. The methods employed for the determination of the configuration of the carbon-nitrogen isomers are based upon the same assumption. An account of these methods must now be given.

1. **Aldoximes.**—One of the principal properties of the aldoximes is the ease with which they lose water, being converted into nitriles :—

$$R.CH:N.OH = R.CN + H_2O$$

Now, the aldoxime may consist of either (I.) or (II.) :—

$$\begin{array}{cc} \begin{array}{r} R\text{—}C\text{—}H \\ \| \quad \\ HO\text{—}N \quad \end{array} & \qquad \begin{array}{l} R\text{—}C\text{—}H \\ \quad \| \\ \quad N\text{—}OH \end{array} \\ \text{(I.)} & \qquad \text{(II.)} \end{array}$$

It is evident that in the compound (I.) the hydrogen and hydroxyl are much further apart than in the case of (II.); and, consequently, we might suppose that in the case of (I.) it would be harder to eliminate the water than would be the case if we were dealing with (II.), where the two constituents are situated nearer together. The case closely resembles that of

the anhydride formation of maleic and fumaric acids. If, then, the Hantzsch-Werner hypothesis were true, we should expect to find differences in the ease with which water is liberated from the two isomers; and, as a matter of fact, such differences do exist. In order to make the difference clear, it is usually found best to employ the acetate of the oxime instead of the oxime itself. When the acetates of the two oximes are warmed with sodium carbonate solution, the one breaks down at once into the nitrile and acetic acid, while the other remains unattacked. Hydrochloric acid has a similar action, but causes transmutation at the same time.[1] From this behaviour it may be inferred that the oxime which yields the nitrile has the hydrogen and hydroxyl nearer to one another than is the case with the undecomposed oxime. We should, therefore, attribute the "syn-" form to the former, and the "anti-" form to the latter.*

Instead of the acetate, the carbanilido-derivative of the oxime may be used in the determination of the configuration, since the one carbanilido-derivative decomposes spontaneously on standing, while the other may be kept for a considerable time without change. The same difference in stability of these compounds is shown when they are heated, the one substance breaking up and yielding a nitrile when its temperature is raised to its melting-point, while the other body must be heated to a higher temperature before the decomposition takes place. The syn-compounds are probably those which break down most easily.

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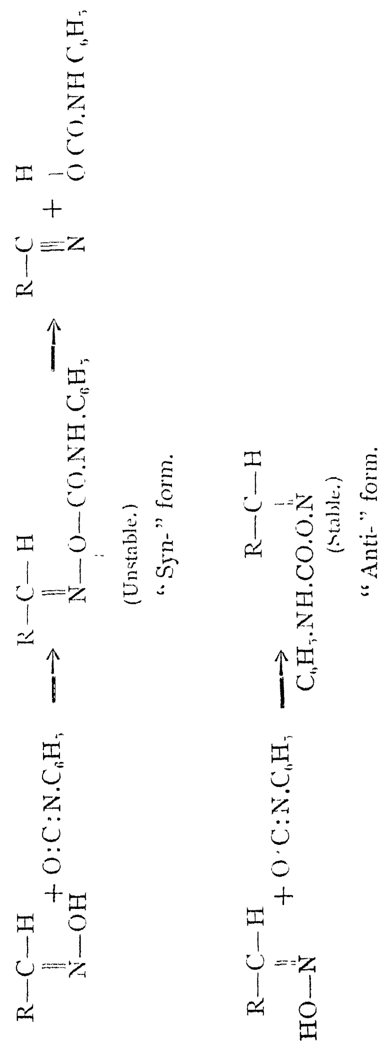
* The practical details of the method are as follows. The aldoxime whose configuration is to be determined is gently warmed with acetic anhydride until it dissolves; after which it is cooled. The solution usually remains clear, but if an oil separates out (indicating nitrile formation and the presence of synaldoxime), it must be filtered off. Solid sodium carbonate is now added to the solution, which causes the precipitation of an oil. In the case of the anti-derivative, this oil is the acetyl derivative of the oxime; in the case of the syn-derivative, it is the nitrile. If caustic soda solution be now added, the acetyl derivative will dissolve, while the nitrile is left unchanged.

[1] Minunni and Vassallo, *Gazzetta*, 26, I., 456 (1896).



From the ease with which aliphatic oximes split off water and become converted into nitriles, it may be concluded that they belong to the syn-variety. Only one or two instances are

known, *e.g.* acetaldoxime and œnanthaldoxime,[1] in which two forms have been isolated; and even in these cases it is not quite certain that the two compounds are stereoisomers.

The oximes of furfurol and thiophene-aldehyde have been isolated in both configurations: the syn-compounds are formed in neutral solution, the anti-compounds when an alkaline solution is used.

When hydroxylamine is allowed to act directly upon an aromatic aldehyde, it appears to produce an anti-aldoxime, which generally can be changed into the syn-form by conversion into the hydrochloride, and subsequent decomposition with sodium carbonate. In the cases where this method of transmutation fails, the syn-form is obtained by the action of sodium ethylate upon the bisnitrosyl compound. Cinnamic aldehyde is an exception to this rule, for here the greater part of the compound formed by direct oximation is the syn-form,[2] while the anti-form is produced in very small quantity.[3]

The aldoximes of most aliphatic series occur in one form only. It is probable that they are syn-compounds, and not merely substances in which the hydroxyl group is symmetrically placed with regard to the hydrogen atom and alkyl group. Or, to express the idea graphically, they exist as (I.) and not as (II.):—

$$\begin{array}{c} R—C—H \\ \quad\;\; \| \\ \qquad N—OH \\ \\ \text{(I.)} \end{array} \qquad\qquad \begin{array}{c} R—C—H \\ \| \\ N \\ | \\ OH \\ \text{(II.)} \end{array}$$

The fatty-aromatic aldoxime, phenyl-acetaldoxime, seems to be of a similar configuration. It exists in only one form, but its acetate has been found in two forms.[4]

It is probable that those ortho-substituted aromatic oximes which exist in only one form are of the anti-configuration.

---

[1] Dollfuss, *Ber.*, **25**, 1916 (1892); Goldschmidt and Zanoli, *ibid.*, **25**, 2596 (1892).

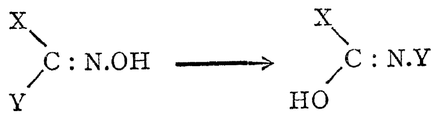
[2] Dollfuss, *ibid.*, **25**, 1919 (1892).

[3] Bamberger and Goldschmidt, *ibid.*, **27**, 3428 (1894).

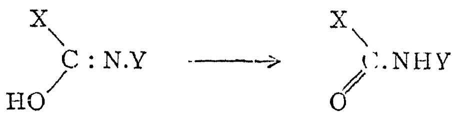
[4] Dollfuss, *ibid.*, **25**, 1910 (1892).

This has been proved in the cases of *o*-tolylaldoxime,[1] *o*-anisaldoxime,[2] and *o*-hydroxybenzaldoxime.[3] To the anti-form belong also meta- and para-hydroxybenzaldoximes.

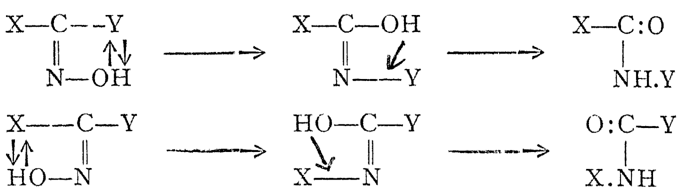
2. Ketoximes.—When a ketoxime is treated with certain reagents (sulphuric acid, hydrochloric acid, acid chlorides and anhydrides, phosphorus pentachloride), it undergoes a peculiar intramolecular change called the Beckmann rearrangement,[4] which occurs in two stages, the first stage being an exchange of structural position between the hydroxyl and one of the radicals united to the doubly linked carbon atom :—



This intermediate compound is then rearranged into an acid amide :—



If we consider what will happen in the case of two stereoisomeric ketoximes, it will be evident that each body will give a different product; since in the one case the one group is nearest the hydroxyl, while in the other case it is the second radical of the ketone which lies on the same side of the molecule as the hydroxyl :—



[1] Dollfuss, *Ber.*, **25**, 1921 (1892).

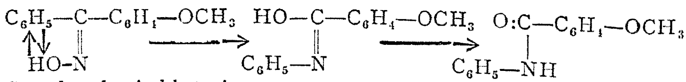
[2] Dollfuss, *ibid.*, **25**, 1933 (1892).

[3] Each, *ibid.*, **16**, 1780 (1883); Beckmann, *ibid.*, **23**, 3320 (1890); Dollfuss, *ibid.*, **25**, 1925 (1892).

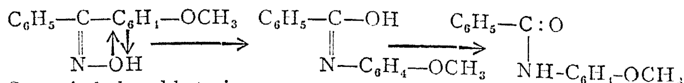
[4] Beckmann, *ibid.*, **19**, 988 (1886); **20**, 506, 2580 (1887); **24**, 4018 (1891).

Thus in the one case the amide of the acid X.COOH is formed, while in the second instance the amide of Y.COOH is produced; from which we may deduce that whichever radical goes to form the acid part of the final product was situated in the anti-position to the hydroxyl in the original compound.

A concrete example may be given. There are two stereoisomeric *p*-methoxy-benzophenone oximes known. The one, when subjected to the Beckmann change, yields the anilide of anisic acid, while the second isomer produces benzoic aniside. From the steric point of view, these results are explained as shown below:—



Syn-phenyl-anisyl ketoxime. Anisic anilide.



Syn-anisyl-phenyl ketoxime. Benzoic aniside.

It has been observed that some reagents which produce the Beckmann change have also the faculty of transmuting the one isomer into the other under the same conditions. Such substances as concentrated sulphuric acid, acetyl chloride, or a mixture of acetic acid, acetic anhydride, and hydrochloric acid, cannot, therefore, be employed in configuration determinations, as their use would introduce a fresh element of uncertainty into the problem. The best method is to treat an ethereal solution of the oxime with phosphorus pentachloride, keeping the temperature below $-20°$ C.[1]

The oximes of saturated aliphatic ketones have, up to the present, been observed to occur in one form only. When these oximes are subjected to the Beckmann change, a mixture of the two possible products is produced; and it has not yet been decided whether this result is due to the presence of a mixture of isomeric oximes in the original compound, or to

[1] Hantzsch, *Ber.*, **24**, 22 (1891).

a partial transmutation taking place while the reaction is in progress. It is quite possible that the hydroxyl group in these cases does not lie near either of the two alkyl radicals, but instead takes up a position midway between the two, as shown in the formula below :—

$$\begin{array}{c} R\text{—}C\text{—}R' \\ \| \\ N \\ | \\ OH \end{array}$$

In this case, when the Beckmann rearrangement came into play, there would be no reason why half the substance should not be drawn to the one side of the molecule, while the other half reacted in the opposite way. This also would produce a mixture of the isomers in the reaction-product.

Some cases of stereoisomerism have been observed among the unsaturated ketones of the aliphatic series,[1] so that it appears that the introduction into the molecule of a double bond between two carbon atoms tends to favour the production of isomerism. This is probably due to the change in chemical character brought about when a saturated radical is converted into an unsaturated one.

The oxime of the alicyclic ketone hexahydropropio-phenone, C_6H_{11}—CO—C_2H_5, apparently has the formula :—

$$\begin{array}{rcl} C_6H_{11}\text{—} & C & \text{—}C_2H_5 \\ & \| & \\ HO\text{—} & N & \end{array}$$

When an aromatic nucleus is introduced into the ketonic structure, the possibility of stereoisomerism occurring appears to be increased, for several oximes of fatty-aromatic ketones have been obtained in two forms: *e.g.* benzil monoxime,[2]

---

[1] Harries and Jablonski, *Ber.*, **31**, 1371 (1898); Knoevenagel and Goldschmidt, *ibid.*, 2465; Harries, *ibid.*, **32**, 1320 (1899).

[2] V. Meyer and Auwers, *ibid.*, **22**, 540 (1889); Beckmann and Koester, *Annalen*, **274**, 6 (1893)

hexa-hydro-benzophenone oxime,[1] benzoin oxime,[2] and ω-bromo-acetophenone oxime.[3]

When both the radicals attached to the carbonyl group of a ketone are aromatic, stereoisomerism in the oximes may be expected almost as a matter of course, when the structure is suitable. By far the greater number of the known cases of stereoisomerism in the oxime series come under this head.

A few oximes of ketonic acids have been isolated in two stereoisomeric forms; and it may be interesting to indicate how the configurations of two of these oximido-acids were determined.

When the acetate of the β-phenyloximido-acetic acid is treated with sodium carbonate, it yields benzonitrile quantitatively; and thus resembles a synaldoxime in behaviour. The acetyl derivative of the α-isomer, on the other hand, when similarly treated, merely regenerates the original oximido-acid. The configurations of the two isomers are therefore probably those shown below:—

$$\begin{array}{rcl} C_6H_5— & C & —COOH \\ & \| & \\ & N & —OH \end{array} \qquad\qquad \begin{array}{rcl} C_6H_5— & C & —COOH \\ & \| & \\ HO— & N & \end{array}$$

β-isomer. α-isomer.

As a general rule, it may be said that those oximido-acids which have the carboxyl and hydroxyl groups in the syn-position to one another lose carbon dioxide from the carboxyl group less readily than is the case with the other series of stereoisomers. From this it was deduced that the acid produced by the action of nitrous acid upon succinylo-succinic ester had the configuration:—

$$\begin{array}{rcl} EtO.CO. & C & .CH_2.COOH \\ & \| & \\ HO. & N & \end{array}$$

[1] Scharvin, *Ber.*, **30**, 2862 (1897).

[2] Werner, *ibid.*, **23**, 2333 (1890).

[3] Korten and Scholl, *ibid.*, **34**, 1902 (1901).

The second isomer was produced by the action of hydroxylamine upon oxalacetic ester; and to it was attributed the configuration :—

$$\begin{array}{rll} \mathrm{EtO.CO.} & \mathrm{C} & \mathrm{.CH_2.COOH} \\ & \| & \\ & \mathrm{N.OH} & \end{array}$$

Confirmatory evidence was found in the fact that the oxime of acetoacetic ester which possesses the configuration :—

$$\begin{array}{rll} \mathrm{CH_3—} & \mathrm{C} & \mathrm{—CH_2—COOEt} \\ & \| & \\ & \mathrm{N—OH} & \end{array}$$

gives a violet coloration with ferric chloride, which coloration is given by the second isomer of oximido-succinic acid. The first isomer does not give this violet colour, but only a yellow one.

The configuration of the oxime of acetoacetic ester is deduced from the ease with which it forms an oxazolone derivative :—

$$\begin{array}{rll} \mathrm{CH_3.} & \mathrm{C} & \mathrm{—CH_2—COOEt} \\ & \| & \\ & \mathrm{N—OH} & \end{array} \longrightarrow \begin{array}{rlcc} \mathrm{CH_3—} & \mathrm{C} & \mathrm{—CH_2—} & \mathrm{CO} \\ & \| & & | \\ & \mathrm{N} & \text{———} & \mathrm{O} \end{array}$$

Nothing definite is known as to the configurations of those quinone monoximes which have been isolated in two forms.

In the course of his researches on the benzhydroximic acids, Lossen[1] discovered a series of isomers which, according to him, show differences in character which cannot be well explained by any difference in their structures. It seems very probable that here again the isomerism is of a steric type, and that the two compounds are space isomers of the following configurations :—

$$\begin{array}{rll} \mathrm{R—} & \mathrm{C} & \mathrm{—OX} \\ & \| & \\ \mathrm{HO—} & \mathrm{N} & \end{array} \qquad\qquad \begin{array}{rll} \mathrm{R—} & \mathrm{C} & \mathrm{—OX} \\ & \| & \\ & \mathrm{N} & \mathrm{—OH} \end{array}$$

[1] Lossen, *Annalen*, **281**, 169 (1894).

in which X may be either an acyl or an alkyl radical The cases in which the evidence in favour of this view is strongest are furnished by the methyl- and ethyl-benzhydroximic acids. When subjected to Beckmann's reaction, the isomers with the lower melting-points give the ordinary change and produce aryl-urethanes; while those with the higher melting-points merely give phosphoric esters of the original compound. This behaviour can be explained as follows:—

$$\begin{array}{c} C_6H_5\text{—}C\text{—}OEt \\ \Vert \\ HO\text{—}N \end{array} \longrightarrow \begin{array}{c} HO\text{—}C\text{—}OEt \\ \Vert \\ C_6H_5\text{—}N \end{array} \longrightarrow \begin{array}{c} O{:}C\text{—}OEt \\ \vert \\ C_6H_5\text{—}NH \end{array}$$

$$3\begin{array}{l} C_6H_5\text{—}C\text{—}OEt \\ \qquad\ \Vert \\ \qquad\ N\text{-}OH \end{array} + PCl_5 + H_2O = 5HCl + \left[\begin{array}{c} C_6H_5\text{—}C\text{—}OEt \\ \Vert \\ N\text{—}O\text{—} \end{array}\right]_3 PO$$

From this it would appear that the forms with the lower melting-points belong to the syn-series, while the others are anti-varieties.

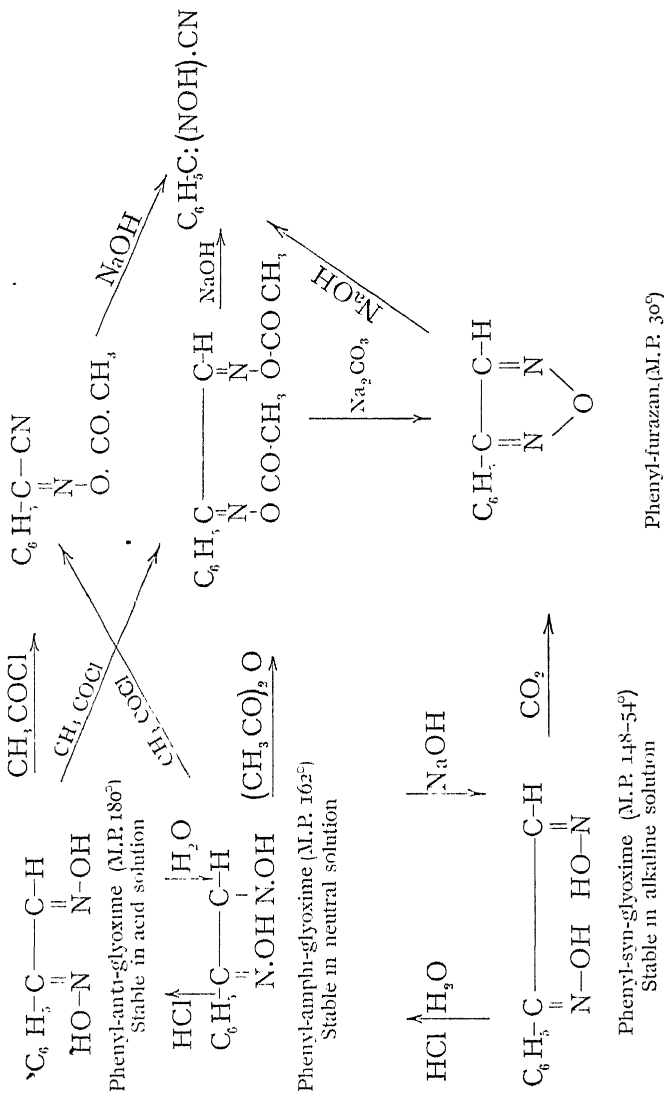
$$\begin{array}{c} C_6H_5\text{—}C\text{—}O\text{—}R \\ \Vert \\ HO\text{—}N \\ \text{(I.)} \end{array} \qquad\qquad \begin{array}{c} C_6H_5\text{—}C\text{—}O\text{—}R \\ \Vert \\ N\text{—}OH \\ \text{(II.)} \end{array}$$

It is obvious that, in the case of (II.), the Beckmann change does not occur, because no real difference in the radicals would be produced by the exchange of a hydroxyl for an ethoxyl group:—

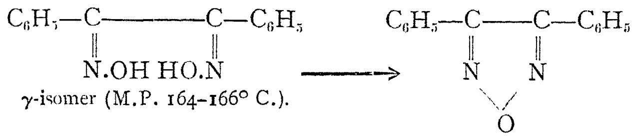
$$\begin{array}{c} C_6H_5\text{—}C\text{—}OR \\ \Vert \\ N\text{—}OH \end{array} \longrightarrow \begin{array}{c} C_6H_5\text{—}C\text{—}OH \\ \Vert \\ N\text{—}OR \end{array}$$

We must now turn to the class of dioximes. Only a few dioximes of aliphatic ketones are known. They are not of very much importance.

Not many dioximes of fatty-aromatic ketones have been isolated in stereoisomeric forms. The following table gives an idea of how the configurations are determined:—

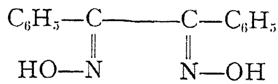

Phenyl-anti-glyoxime (M.P. 180°)
Stable in acid solution
Phenyl-amphi-glyoxime (M.P. 162°)
Stable in neutral solution
Phenyl-syn-glyoxime (M.P. 148–54°)
Stable in alkaline solution
Phenyl-furazan (M.P. 30°)
CH₃COCl
(CH₃CO)₂O
NaOH
CO₂
HCl
H₂O
Na₂CO₃

Among the dioximes of aromatic ketones, the most important of all are the dioximes of benzil, which exist in the three forms syn-, amphi-, and anti-. The configurations of the isomers have been deduced from the degree of ease with which they form diphenyl-furazan. When the ether of one isomer (the γ-isomer) is hydrolysed, the furazan derivative is produced in the process. This proves that the two hydroxyl groups of the dioxime must be in close proximity to one another, and it is concluded that the isomer in question must be the syn-form.



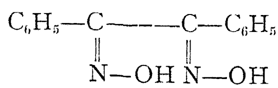
γ-isomer (M.P. 164–166° C.).

Another isomer, the β-compound, which appears to be the most stable of all, is produced whenever the reaction of oximation is energetic; it is therefore supposed to be the anti-form, which gives least opportunity for anhydride formation :—



M.P. 206–207° C.

The α-isomer, whose stability appears to lie between those of the other two, is probably the amphi-form :—

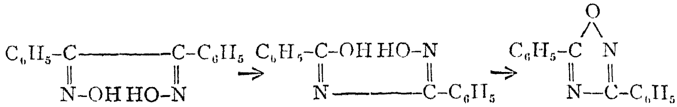


M.P. 237° C.

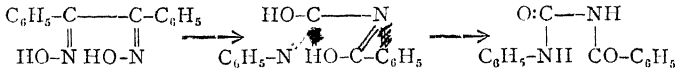
Further evidence is supplied by the results of the Beckmann change upon the three bodies, but it does not agree with that given above.[1] β-benzil-dioxime gives oxanilide :—

[1] Beckmann and Koester, *Annalen*, **274**, 15 (1893).

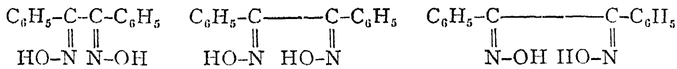
α-benzil-dioxime yields dibenzenylazoxime :—



γ-benzil-dioxime produces benzoyl-phenyl-urea :—

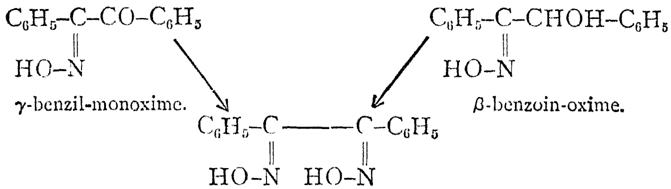


From these results the following configurations are deducible :—



(β.) (γ.) (α.)

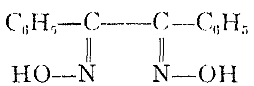
These configurations agree with those previously considered only as regards the β-isomer. The weight of evidence, however, appears to lie on the side of the second set of deductions. For if we consider two syntheses of the γ-isomer, in the one case from γ-monoxime and in the other case from β-benzoin-oxime, both of whose configurations have been determined by the action of Beckmann's change, we find the following :—



γ-benzil-monoxime. β-benzoin-oxime.

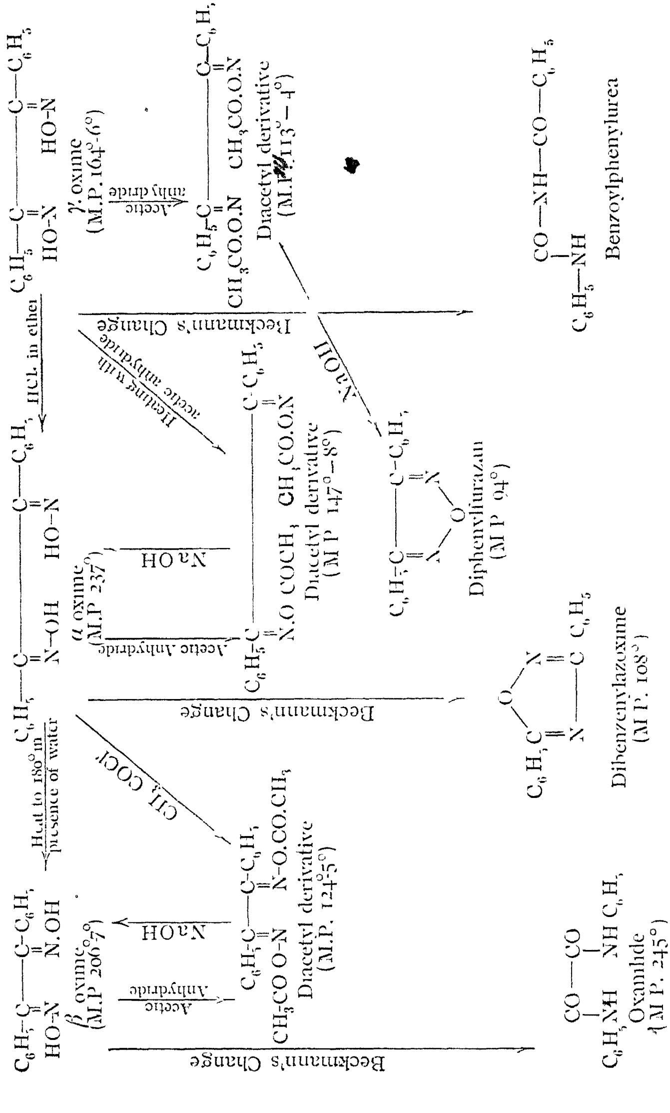
γ-dioxime.

This is the only possible formula if one of the hydroxyl groups is in a syn-position to a phenyl group; the only other possible formula which fulfils this condition being that which has been definitely assigned to the β-isomer :—



β-dioxime.

A table showing the various changes undergone by the three isomers may now be given: —



No definite configurations have been assigned to the other dioximes of the aromatic ketones, though several attempts have been made to deduce their configurations from analogy with the dioximes of benzil.

The case of the dioximes of camphorquinone may be mentioned, as here all the four possible forms have been isolated, the first three by Manasse,[1] and the fourth by Angelico.[2] Forster[3] has studied the four isomers and finds the following :—

	M.P.	$[\alpha]_D$ in alcohol.	$[\alpha]_D$ in 2 % NaOH.	1 gram dissolves in
α-dioxime	201°	− 66·6°	− 98·3°	40·0 cc. absol. alcohol
β- ,,	248°	—	− 24·1°	59·0 ,, ,,
γ- ,,	135°	+ 22·4°	+ 12·6°	1·0 ,, ,,
δ- ,,	199°	+ 75·4°	+ 83·6°	12·4 ,, ,,

3. Hydrazones.[4]—Though it is practically certain that some cases of isomerism in the hydrazone series are due to spacial differences between the two isomers, no certain method has yet been devised by which the configuration of the isomers can be deduced. The methods which can be employed in the cases of the oximes cannot be utilised in the case of the hydrazones.

[1] Manasse, *Ber.*, **26**, 243 (1893).

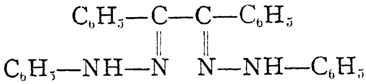
[2] Angelico, *Atti R. Accad. Lincei*, [5] **9**, II., 47 (1900).

[3] Forster, *Trans.*, **83**, 514 (1903).

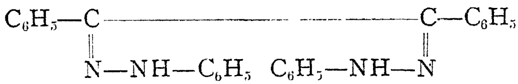
[4] Reference may be made to papers on the phenylhydrazones of acetaldehyde [Fischer, *Ber.*, **29**, 793 (1896)]; anisyl-phenyl-ketone [Hantzsch and Kraft, *ibid.*, **24**, 3526 (1891); Auwers and V. Meyer, *ibid.*, **24**, 4226 (1891); Claus, *J. pr. Chem.*, [2] **45**, 377 (1892); **47**, 267 (1893); Hantzsch, *Ber.*, **25**, 1699 (1892)]; benzoin [Pickel, *Annalen*, **232**, 229 (1886); Vogtherr, *Ber.*, **25**, 637 (1892); Smith and Ransom, *Am. Chem. J.*, **16**, 108 (1894)]; salicylic aldehyde [Biltz, *Ber.*, **27**, 2288 (1896)]; benzaldehyde [Thiele and Pickard, *ibid.*, **31**, 1249 (1898)]: and on the osazones of benzil [Ingle and Mann, *Trans.*, **67**, 606 (1895); Minunni and Rapp, *Gazzetta*, **26**, [I.] 444 (1896); Biltz, *Annalen*, **305**, 165 (1899); Biltz and Amme, *ibid.*, **321**, 1 (1902)]; salicylic aldehyde [Biltz, *ibid.*, **305**, 179 (1899)]; anisaldehyde [Biltz, *ibid.*, **308**, 7 (1899)]. This list is merely one of illustrative examples, and is not complete.

In one or two cases attempts have been made to prove the configuration of certain derivatives, and it may be interesting to describe them here.

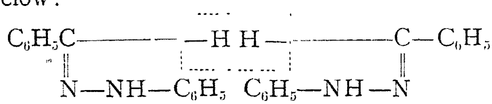
From analogy it is deduced that the benzil-osazone having the highest melting-point (β, M.P. 225° C.) is the anti-isomer :—



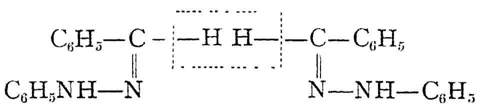
while the isomer with the lower melting-point (α, M.P. 208° C.) is the syn-isomer :—



Now when the α-isomer of benzaldehyde phenylhydrazone is gently oxidised, it yields syn-benzil-osazone; while β-benzaldehyde phenylhydrazone gives the anti-isomer. From this it is deduced that the formulæ for the two isomers must be those shown below :—



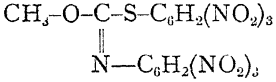
(α.)

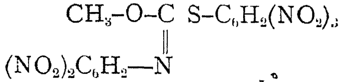


(β.)

It does not appear at all likely that the configuration of the hydrazones can be determined by the crude methods at present at our disposal.

Crocker[1] has isolated two forms of picryl-picrimino-thiocarbonic methyl ester, which appear to have the configurations :—





[1] Crocker, *Trans.*, **81**, 436 (1902).

4. **Anils.**—The question of the existence of stereoisomeric anils appears to be as yet unsettled. On the one hand, Simon[1] maintains that these isomers do not exist; while Miller and Plochl[2] state that they have obtained derivatives of the type:—

$$\begin{array}{c} R—C—R_1 \\ \| \\ \;\;\; N—R_2 \end{array}$$

Eibner and Peltzer[3] isolated two isomers which, according to Miller and Plöchl's view, would be of the type:—

$$\begin{array}{llll} CH_3—CH & \text{———} & C—CH_3 \\ \quad\;\;| & & \| \\ C_6H_5—NH & C_6H_5— & N \end{array} \qquad \begin{array}{llll} CH_3—CH & \text{——} & C—CH_3 \\ \quad\;\;| & & \| \\ C_6H_5—NH & & N—C_6H_5 \end{array}$$

Eibner, however, prefers to consider this as a case of ethylene isomerism;[4] and supposes them to have the constitution and configurations given below:—

$$\begin{array}{lll} CH_3–CH & \text{——} & C–H \\ \quad\;\;| & & \| \\ C_6H_5–NH & H– & C–NH.C_6H_5 \end{array} \qquad \begin{array}{llll} CH_3–CH & \text{————} & & C–H \\ \quad\;\;| & & & \| \\ C_6H_5–NH & C_6H_5\text{-}NH & & C\;\;H \end{array}$$

Hantzsch and Hornbostel[5] found certain isomers which they proved were stereoisomeric; and, later, Hantzsch and Schwab[6] isolated two isomeric forms of benzylidene-*p*-toluidine to which they ascribed the stereoisomeric configurations:—

$$\begin{array}{ll} C_6H_5— & C—H \\ & \| \\ & N—C_6H_4—CH_3 \end{array} \qquad \begin{array}{rl} C_6H_5— & C—H \\ & \| \\ CH_3—C_6H_4— & N \end{array}$$

It is evident that the matter is still unsettled.

5. **Semicarbazones, Thiosemicarbazones, and Thiosemicarbazides.**—In 1895, Wallach[7] discovered certain semicarbazones

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[1] Simon, *Compt. rend.*, **118**, 1345 (1894); *Bull. Soc. Chim.*, [3] **13**, 334, 374 (1895); *Ann. Chim. Phys.*, [7] **9**, 433 (1896).

[2] Miller and Plochl, *Ber.*, **27**, 1296 (1894).

[3] Eibner and Peltzer, *ibid.*, **33**, 3461 (1900).

[4] Eibner, *Annalen*, **318**, 58 (1901).

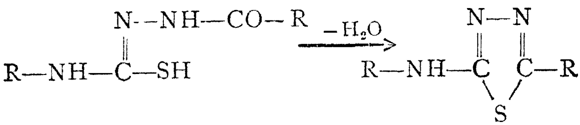
[5] Hantzsch and Hornbostel, *Ber.*, **30**, 3003 (1897).

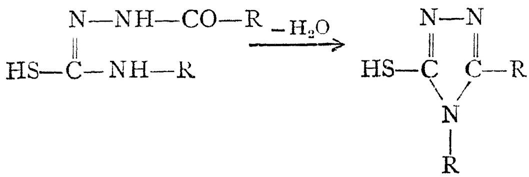
[6] Hantzsch and Schwab, *ibid.*, **34**, 822 (1901).

[7] Wallach, *ibid.*, **28**, 1955 (1896).

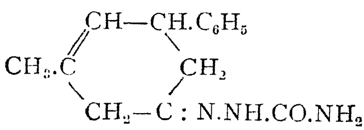
in the terpene series whose properties appeared to agree with the idea that they were stereoisomers.

In the following year, Freund[1] pointed out that a proof of the existence of stereoisomeric thiosemicarbazones was furnished by the fact that when one molecule of water was withdrawn from certain members of the series, two isomeric substances were formed. This could be explained if the following space formulæ were adopted:—





Knoevenagel and Goldsmith[2] found that the semicarbazone of methyl-phenyl-cyclohexenone existed in two stereoisomeric forms, each of which has this structure:—

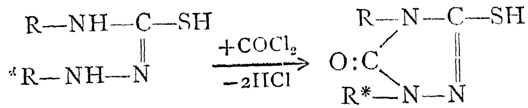


Posner[3] has discovered two stereoisomeric mono-semicarbazones of benzil.

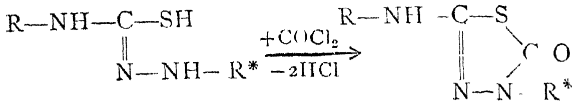
The thiosemicarbazides have been studied very thoroughly by Marckwald.[4] He found that in attempting to distinguish between the isomers when only a very small quantity of the substance was available, it was best to use phosgene as a

[1] Freund, *Ber.*, **29**, 2483 (1896).
[2] Knoevenagel and Goldsmith, *ibid.*, **31**, 2474 (1898)
[3] Posner, *ibid.*, **34**, 3979 (1901).
[4] Marckwald, *ibid.*, **32**, 1081 (1899); compare **25**, 3098 (1892).

reagent. In the case of the labile anti-form (I.), the reaction produces an ammoniacal solution which yields with hydrochloric acid a voluminous precipitate of imidobiazolonyl mercaptan; the syn-form (II.), on the other hand, produces a thiobiazolone derivative.



(I.)



(II.)

These relations hold good in the case where R is a phenyl radical. If the R group, marked with an asterisk, be an acetyl radical, the thiosemicarbazide exists in one form only, and during the reaction products are produced which seem to indicate a change from the syn- into the anti-form. Those compounds which have an alkyl group in the position marked by the asterisk appear to exist only in the anti-form. The examination of a large number of cases enabled Marckwald to show that the following rules held good :—

I. Phenylhydrazine reacts with allyl thiocyanate to form a thiosemicarbazide of the anti-form, which goes over into the syn-form on heating or when treated in alcoholic solution with a trace of hydrochloric acid.

II. The same holds good if there be a substituent in the para-position of the phenylhydrazine.

III. If there be a substituent in the hydrazine's ortho- or meta-position, only stable thiosemicarbazides of the syn-form are produced.

IV. The nature and position of substituents in the allyl thiocyanate have no effect on the reaction.

V. The labile compounds of the anti-form have a lower melting-point than the stable syn-forms.

VI. Secondary hydrazines do not form stereoisomeric compounds.

Busch and Holzmann[1] dispute the correctness of Marckwald's view, and attribute the isomerism to a wandering of the phenyl isocyanate nucleus.

6. Chlorimides, etc.—Stieglitz,[2] in 1896, though unable to isolate two forms of chlorimido-benzoic ester, was led to conclude that the isomer isolated by him corresponded to the anti-form :—

$$\begin{array}{c} C_6H_5-C-O.Et \\ \| \\ N-Cl \end{array}$$

Stieglitz and Earle[3] obtained two stereoisomeric compounds by the following series of reactions. By treating *m*-nitrobenzamide with sodium hypochlorite, they obtained *m*-nitrobenzoyl-chloroamide, $NO_2.C_6H_4.CO.NHCl$, which, when allowed to react with diazo-methane, gives the α-modification of methyl-chlorimido-*m*-nitrobenzoate, $NO_2.C_6H_4.C(OCH_3):N.Cl$. This modification crystallizes in long prisms or rectangular plates of melting-point 86·5°–87·5° C. When this α-compound is treated with hydrochloric acid, it gives a hydrochloride; and if this hydrochloride is added to a large excess of sodium hypochlorite at 30° C., a mixture of the α- and β-forms of the chlorimide is obtained, from which the β-compound can be extracted by repeated crystallization from a mixture of chloroform and petroleum ether. The β-modification crystallizes in thin rhombohedric plates of melting-point 81°–82° C. With hydrochloric acid it gives the hydrochloride of methyl-chlorimido-*m*-nitrobenzoate. The two isomers have the same molecular weight; they are stable at 80° C., or even for a few minutes at 140° C. Their configurations may be represented by :—

$$\begin{array}{c} NO_2.C_6H_4-C-OCH_3 \\ \| \\ Cl-N \qquad\quad \end{array} \qquad\qquad \begin{array}{c} NO_2.C_6H_4-C-OCH_3 \\ \| \\ \qquad\quad N-Cl \end{array}$$

---

[1] Busch and Holzmann, *Ber.*, **34**, 320 (1901).

[2] Stieglitz, *Amer. Chem. J.*, **18**, 751 (1896).

[3] Stieglitz and Earle, *ibid.*, **30**, 399 (1903).

No transmutation of one isomer into the other could be effected. If the stereoisomerism be denied, the only alternative appears to be to suppose that the one form is produced from the other by Beckmann's rearrangement. This is quite improbable, however, as Stieglitz and Earle found that no such change could be brought about in either of the isomers. The stereochemical explanation appears to be the only one which explains the facts. This is a most important case, from the point of view of the Hantzsch-Werner hypothesis, for here the possibility of tautomerism is reduced to a minimum, there being no possibility of constructing formulæ analogous to those put forward to explain the oxime isomerism by structural differences.

Hantzsch[1] has endeavoured, without success, to isolate stereoisomeric urethanes of the type :—

$$\begin{array}{l} a \\ \quad\diagdown \\ \qquad C : N.COOEt \\ \quad\diagup \\ b \end{array}$$

Walther[2] suggests that of the four known methenyl-phenyl-*p*-tolylamidines two are stereoisomers of the type :—

$$\begin{array}{ccc} C_6H_5.NH—C—H & \qquad & C_6H_5.NH—C—H \\ \quad\quad\quad\quad\ \ \| & & \quad\quad\quad\quad\ \ \| \\ \quad\quad\quad\quad\ \ N—C_6H_4.CH_3 & & CH_3.C_6H_4—N \end{array}$$

Cohen[3] has applied the Hantzsch-Werner theory to the case of the acid amides, and comes to the following conclusions. Those amides which crystallize in prisms and give silver salts belong to the anti-series; those which crystallize in plates and give no silver salts belong to the syn-form. All compounds derived from ammonia or fatty amines are anti-isomers, while amides produced from aromatic amines are syn-compounds.

Cordier[4] finds that guanidine picrate exists in two forms, one being stable, the other labile. The isomers differ in solubility and crystalline form, but appear to be otherwise

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[1] Hantzsch, *Ber.*, **25**, 2025 (1892).

[2] Walther, *J. pr. Chem.*, [2] **55**, 41, 552 (1897).

[3] Cohen, *Chem. News*, **70**, 100 (1894).

[4] Cordier, *Verhandl. d. Ges. deut. Ntf. u. Aertzte*, 1904, II. 105.

identical. Solutions of both isomers are inactive as regards polarized light. The author supposed them to be stereoisomers of the following type :—

$$\begin{array}{ll} NH_2.C.NH_2.OH.C_6H_2(NO_2)_3 & NH_2.C.NH_2.OH.C_6H_2(NO_2)_3 \\ \quad\;\; \| & \quad\;\; \| \\ \quad\;\; N-H & \quad H-N \end{array}$$

Stable form (plates). Labile form (needles).

§ VI. *METHODS OF PRODUCING CARBON-NITROGEN STEREOISOMERS.*

1. Aldoximes.—Though many cases of stereoisomeric aldoximes are known, in only a very few of them has it been found that a mixture of both isomers is produced in the reaction by which they are synthesised, *e.g.* propionaldoxime, furfuraldoxime, thiophenaldoxime, and cinnamaldoxime. In a few cases the relative quantities of the two isomers produced may be controlled by varying the conditions of experiment. In the case of furfuraldoxime, for instance, it is found that if the synthesis be carried out in alkaline solution, the major part of the reaction-product consists of the anti-form; while when neutral solution is used, the syn-form preponderates. The transmutation of one isomer into the other by means of heat can be accomplished in the case of acetaldoxime.

The most common method of obtaining two isomers is to transmute the one form into the other. The methods employed will be described in a separate section (see § VIII.).

Another method consists in the depolymerisation of the bisnitrosyl compound, which is obtained by the oxidation of the corresponding mono-hydroxylamine :—

$$\begin{array}{l} R-CH_2-NH-OH \\ R-CH_2-NH-OH \end{array} + 2O = 2H_2O + (R.CH_2.NO)_2$$

When acted on by sodium ethylate, these bisnitrosyl compounds break down into a mixture of the syn- and anti-forms of the aldoxime :—

$$(R.CH_2.NO)_2 = R.CH : NOH \text{ (syn-)} + R.CH : NOH \text{ (anti-)}$$

Comstock[1] has shown that aldoximes have the faculty of forming addition-compounds with cuprous chloride or bromide, which addition-compounds, on decomposition, yield the syn-form of the oxime. They therefore form a means of preparing synaldoximes.

2. Ketoximes.—When ketones are oximated in alkaline solution, a mixture of the two stereoisomers is produced. They can be separated from one another by fractionally precipitating an alcoholic or acetic acid solution of the mixture by means of water. Under these conditions the isomer with the higher melting-point is first precipitated.

Stereoisomeric oximido-acids and alkyl-hydroximic acids are formed as a mixture of the two configurations which can be separated from one another by fractional crystallization.

3. Hydrazones, etc.—In many cases the action of phenylhydrazine upon a suitable ketone produces a mixture of two stereoisomeric hydrazones, which can be separated from one another by utilising the difference in their solubility. The same is true for the action of phenylhydrazine on keto-chlorides of the type $X—C.Cl_2—Y$.[2]

It has been found possible in some cases to obtain one isomer from the other: this will be dealt with in § VIII.

Too little is known with regard to the semicarbazones and other compounds to allow of any general statements being made as to their properties in this connection.

§ VII. *THE PROPERTIES OF CARBON-NITROGEN STEREOISOMERS.*

1. Physical Properties.—The melting-points of the two isomers are different, just as in the case of ethylene stereoisomers. As a general rule, the syn-oximes have a higher melting-point than the anti-forms, though this is not always the case.

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[1] Comstock, *Amer. Chem. J.*, **19**, 485 (1897).

[2] Hantzsch and Kraft, *Ber.*, **24**, 3511 (1891); Hantzsch and Overton, *ibid.*, **26**, 9 and 18 (1893).

Very little material is available as regards the relative solubility of the two stereoisomeric forms. From the work of Beckmann, Goldschmidt, and others,[1] it seems probable that the form with the higher melting-point (syn-form) has a lower solubility than the anti-form. The same relations appear to hold good in the case of the hydrazones also.

Even less is known of the crystalline form. It is probable that the two isomers have different crystalline forms.[2]

According to Hartley and Dobbie,[3] the absorption spectra of benzsyn-aldoxime and benzanti-aldoxime are identical.

It is found that the affinity constants of two stereoisomeric oximido-acids differ very considerably, and to this extent resemble the acids of the ethylene series. It is found also that substitution has a considerable effect upon the conductivity; and it would seem that this is due to the curving of the carbon chain which makes it possible for hydroxyl and carboxyl groups in the anti-position to each other to approach more closely to one another in the α- and γ-ketoximic acids than they do in the β-compounds.

2. Chemical Properties.—(*a*) *Formation of Addition-compounds with Solvents.*—A point of difference between the two isomers is to be found in the amounts of alcohol or benzene with which they crystallize. For instance, γ-benzil-monoxime crystallizes with half a molecule of benzene; the β- and γ-dioximes crystallize with one molecule of alcohol of crystallization; α-benzil-monoxime and α-benzil-dioxime apparently give no addition-compounds:—

$$\begin{array}{c} C_6H_5—C—C—C_6H_5 \\ \quad\ \ \| \quad\ \| \\ HO—N \quad O \\ + \tfrac{1}{2}C_6H_6 \end{array} \qquad\qquad \begin{array}{c} C_6H_5—C———C—C_6H_5 \\ \quad\ \| \qquad\quad \| \\ HO—N\ \ HO—N \\ + C_2H_5OH \end{array}$$

γ-benzil-monoxime. $\qquad$ γ-benzil-dioxime.

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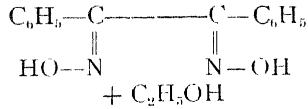
[1] Beckmann, *Ber.*, **23**, 1686 (1890); Goldschmidt, *ibid.*, **23**, 2170 (1890); Goldschmidt and Kjellin, *ibid.*, **24**, 2550 (1891); Behrend and König, *Annalen*, **263**, 349 (1891).

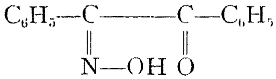
[2] Goldschmidt, *Ber.*, **23**, 2173 (1890).

[3] Hartley and Dobbie, *Trans.*, **77**, 509 (1900).

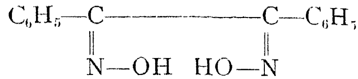


β-benzil-dioxime.

No addition-compounds are formed by:—



α-benzil-monoxime.

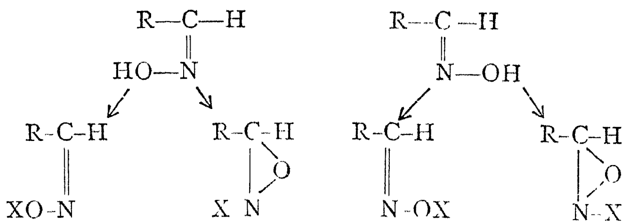


α-benzil-dioxime.

It appears, therefore, as if the property of addition depended on the hydroxyl being in the syn-position to the phenyl radical.

(*b*) *Carbanilide Formation.*—A somewhat similar instance of the difference between the isomers is found in the action of isocyanates upon the syn- and anti-forms of aldoximes. In this case the syn-substances often give addition-products; while only isolated cases have been observed in the series of anti-compounds.[1] No differences have been observed in the case of the ketoximes.

(*c*) *The Alkylation of Oximes.*—It has been found that when an alcoholic solution of an oxime is treated with sodium ethylate and an alkyl iodide, the products of the reaction vary according as a syn- or an anti-isomer is used as a starting material. The formulæ below show the results which are generally observed:—



Chief product Bye-product. Bye-product. Chief product.

(*d*) *Breakdown of Aldoximes and α-Oximido-acids to*

[1] Goldschmidt and Rietschoten, *Ber.*, **26**, 2098 (1893).

Nitriles.—This has already been described in the case of the aldoximes. The case of the α-oximido-acids is almost the same; the agents used being acetic anhydride, or alkali carbonates. The reaction takes the following form :—

$$\begin{array}{l} C_6H_5\text{—}C\text{—}COOH \\ \quad\quad\;\; \| \\ \quad\quad\;\; N\text{—}O.CO\text{—}CH_3 \end{array} \quad = \quad \begin{array}{l} C_6H_5\text{—}C \\ \quad\quad\;\; ||| \\ \quad\quad\;\; N \end{array} \; + \; \begin{array}{l} CO_2 \\ \\ HO.CO\text{—}CH_3 \end{array}$$

(*c*) *The Beckmann Rearrangement.*—The effect of stereoisomerism upon this reaction has already been fully dealt with. It might be well to point out that, though the Beckmann method is the only one by which the configuration of oximes can be deduced with any certainty, yet the results arrived at by this method cannot be relied upon completely.

§ VIII. *THE TRANSMUTATION OF CARBON-NITROGEN STEREOISOMERS.*

1. **General.**—In the case of the stereoisomeric ethylene compounds, it was pointed out that the relative stability of the two isomers depended upon the strengths of the attractions which the various groups in the molecule exerted upon each other. The same holds good in the case of the isomers containing a double bond between a carbon and a nitrogen atom. For example, in the case of the compound shown below, the isomer (I.) will be more stable than the isomer (II.) when the attraction of the group Z is stronger for X than for Y.

$$\begin{array}{c} X\text{—}C\text{—}Y \\ \| \\ Z\text{—}N \quad\; \\ \text{(I.)} \end{array} \qquad\qquad \begin{array}{c} X\text{—}C\text{—}Y \\ \| \\ \quad\; N\text{—}Z \\ \text{(II.)} \end{array}$$

It may happen, however, that the attraction of Z for Y is, under ordinary conditions, sufficiently strong to retain the two groups in proximity to one another, though not strong enough to bring them together again if they are once disturbed by outside influences. In that case, the isomer (II.) would be a labile form, liable to conversion into the more stable form (I.)

as soon as any disturbance took place in the intramolecular system. Such disturbances may be brought about in many ways, either by physical or chemical agency. A very complete study of the case of the series of compounds of the type $\begin{array}{l} X \\ Y \end{array}\!\!>C = N.NH.Z$ has been made by Bamberger and Schmidt.[1]

2. Transmutation by Physical Influences.—In many cases, when the labile isomer is heated it is converted into the stable form. The syn-form of phenyl-xylyl-oxime :—

$$\begin{array}{c} C_6H_5\text{—}C\text{—}C_6H_3(CH_3)_2 \\ \quad\;\; \Vert \\ HO\text{—}N \end{array}$$

produces the anti-isomer.[2] When one modification of the chlorophenylhydrazone of aceto-acetic ester (M.P. 62–63° C.) is melted, and then allowed to cool slowly, it is changed into the other isomer (M.P. 80–83° C.).[3] The hydrazone of anil-pyruvylpyruvinic ester :—

$$\begin{array}{rl} C_6H_5\text{—}N = & C\text{—}CH_3 \\ & \vert \\ C_6H_5NH\text{—}N = & C - CH_2\text{—}CO\text{—}COOC_2H_5 \end{array}$$

yields a second isomer when it is heated to 200° C.[4] Benzil-monoxime can be converted into another isomer by heating to 100° C. with alcohol in a sealed tube for eight hours.[5] Benzoin oxime[6] of M.P. 99° C., when heated with alcohol to 180° C., has its melting-point raised to 151° C.; and when *p*-bromo-benzophenone oxime is warmed in alcoholic solution, the melting-point changes from 107–111° C. to 165–166° C.[7] Para-ethyl-benzophenone oxime requires only warming;[8] *p*-iodo- and *m*-bromo-benzophenone need to be heated for

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[1] Bamberger and Schmidt, *Ber.*, **34**, 2003 (1901).
[2] Bartolotti and Linari, *Gazzetta*, **32**, II., 271 (1902).
[3] Kjellin, *Ber.*, **30**, 1966 (1897).
[4] Simon, *Compt. rend.*, **135**, 630 (1903).
[5] Auwers, *Entwicklung der Stereochemie*, p. 61.
[6] Werner, *Ber.*, **23**, 2335 (1890).
[7] Schaefer, *Annalen*, **264**, 164 (1891).
[8] Smith, *Ber.*, **24**, 4032 (1891).

twelve and twenty-four hours to about 150° C. before the change occurs.[1] Ciamician and Silber[2] have shown that when solutions of *o*- and *p*-nitrobenzantialdoxime in benzene are exposed to the action of light they are converted into the syn-compounds.

The effect of solvents is very marked in some cases. The isomer of papaveraldoxime melting at 235° C. can be converted into the variety melting at 254° C. by crystallizing it several times.[3] Repeated crystallization from alcohol converts the aceto-acetic ester phenylhydrazone of M.P. 62–63° C. into the isomer with M.P. 80–83° C.[4] A reverse change in melting-point is shown when the phenylhydrazone of nitro-valerianic aldehyde is boiled with ligroin; for here an isomer melting at 93° C. is changed to one with M.P. 52° C. The easily soluble *o*-chlorotoluquinone-oxime (M.P. 165° C.), on standing in toluene or alcohol solution, is converted into the less soluble form with M.P. 170° C.[5] The oxime of phenylglyoxylic acid has its melting-point raised from 127° C. to 145° C. by being allowed to stand in either acid or aqueous solution.[6]

It has been found that when some stereoisomers are allowed to stand, they are spontaneously converted into the other isomeric form. This has been observed in the case of *p*-methoxybenzophenone oxime,[7] where the substance with the higher melting-point is converted into one with a lower.

3. Transmutation by Chemical Influences.—When concentrated sulphuric acid is allowed to act upon the anti-form of benzaldoxime, it converts it into benzsynaldoxime; but the reverse change may be brought about by treating the syn-form with dilute acids, when the anti-oxime is produced. This

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[1] Hoffmann, *Annalen*, **264**, 166 (1891), Kottenhahn, *ibid.*, **264**, 170 (1891).

[2] Ciamician and Silber, *Ber.*, **36**, 4268 (1903)

[3] Hirsch, *Monatsh.*, **16**, 830 (1895).

[4] Kjellin, *Ber.*, **30**, 1966 (1897).

[5] Kehrmann and Tichvinsky, *Annalen*, **303**, 15 (1898).

[6] Hantzsch, *Ber.*, **24**, 41 (1891).

[7] Hantzsch, *ibid.*, **24**, 53 (1891).

holds good only in the case of the aldoximes themselves, and is not true for their derivatives. Hydrochloric acid gas converts α-benzil-monoxime into the γ isomer;[1] benzoin oxime of M.P. 99° C. into the isomer with M.P. 151° C.; papaveraldoxime of M.P. 235° C. into that with M.P. 254° C.; and raises the melting-point of the oxime of phenyl-glyoxylic acid from 127° C. to 145° C.[2] It has the same effect in the hydrazone series, converting the lower melting form of pyruvic ester hydrazone into the other isomer.[3] Measurements of the velocity of transmutation of several oximes with hydrochloric acid were made by H. Ley.[4]

In some cases a trace of bromine suffices to convert a solid syn-aldoxime acetate into the anti-acetate.

Many cases are known in which the action of bases is sufficient to bring about the change from one isomer into the other. A few examples may be given here. When methyl-phenyl-cyclohexenone oxime is dissolved in warm caustic soda solution, and the solution then neutralised, the resultant product, after sublimation, is the other isomer; the melting-point being changed from 151° C. to 115° C. Benzoin oxime, when boiled with a dilute solution of aqueous-alcoholic alkali, is changed in the opposite way: the compound melting at 99° C. being converted into the other isomer with a melting-point of 151° C. On the other hand, when *p*-ethyl-benzophenone oxime of melting-point 142° C. is heated to 120° C. with caustic soda and hydroxylamine, it goes over into the substance melting at 108° C. In the case of the hydrazones, it appears that mere heating with excess of phenylhydrazine is sufficient to bring about the transmutation of one isomer into the other; benzil-syn-osazone[5] yields the anti-isomer; piperil-phenylosazone[6] can be changed from the syn- to the anti-configuration. When

[1] Auwers, *Entwicklung der Stereochemie*, p. 61.

[2] Hantzsch, *Ber.*, **24**, 41 (1891).

[3] Simon, *Compt. rend.*, **131**, 682 (1901).

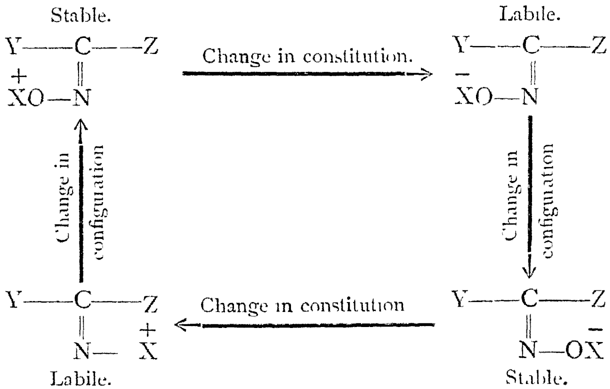
[4] Ley, *Zeit. physikal. Chem.*, **18**, 388 (1895).

[5] Ingle and Mann, *Trans.*, **67**, 606 (1895); Minunni and Rapp, *Gazzetta*, **26**, I., 444 (1896).

[6] Biltz and Wienands, *Annalen*, **308**, 9 (1899).

the acetaldehyde phenylhydrazone melting at 66–69° is treated with caustic soda solution, it is converted into the second isomer, which melts at 98–101° C.

Hitherto we have not considered the effect of a change in chemical constitution in causing an alteration in the configuration; but we must now describe another method of bringing about transmutation, in which this influence is utilised. From what has already been said with regard to the mutual attractions of various groups in a molecule, and their effects upon the configuration of the compound, it will be evident that such a process as acetylation may be used to bring about the transmutation of one isomer into the other. The following scheme expresses the matter graphically:—



Here $\overset{+}{X}$ is supposed to be some electro-positive group or atom like Na; while $\overset{-}{X}$ is an electro-negative group such as an acetyl or benzoyl radical. It is obvious that by replacing $\overset{+}{X}$ by $\overset{-}{X}$, the stability of the two isomers can be reversed; so that the isomer, which in alkaline solution is the more stable of the two, may become the labile isomer when acetylation has been carried out, and the sodium atom replaced by an acetyl group. The reverse change would be produced by the hydrolysis of the acetyl derivative to the simple oxime. The

oxime of phenyl-glyoxylic acid, which melts at 145° C., can be changed to that which melts at 127° C. by this method, using acetyl chloride as the agent;[1] and oximido-succinic acid of melting-point 125° C. can be changed into the lower-melting variety, M.P. 88° C., by the use of acetyl chloride or acetic anhydride.[2] When one stereoisomer of quinone oxime is acetylated or benzoylated, it appears to yield a mixture of two stereoisomeric benzoyl derivatives.[3] The same holds good in the case of the phenylhydrazones also.[4]

In many cases it is found that acetic anhydride and acetyl chloride have different effects upon the same stereoisomer, the anhydride merely acetylating, while the chloride simultaneously changes the configuration and produces the acetyl derivative. It appears most probable that this difference is due to the fact that in one reaction hydrochloric acid is liberated, which acts as a transmuting agent.

Two agents may be mentioned whose use is confined to exceptional cases. It has been found that by treatment with pentachloride of phosphorus at low temperatures, one-third of a given amount of *p*-tolyl-phenyl ketoxime can be converted from the anti- into the syn-phenyl form. The most peculiar instance of all has been observed by Busch,[5] who found that, though all the ordinary methods failed to produce transmutation in the case of the hydrazones of di-thiocarbonic esters:—

$$\begin{array}{l} X—S—C—S—Y \\ \qquad\quad\;\; \| \\ \qquad\quad\;\; N—NH—C_6H_5 \end{array}$$

the desired effect was produced by merely boiling the substances in alcoholic solution with animal charcoal.

4. Transmutation through Intermediate Compounds.—It

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[1] Hantzsch, *Ber.*, **24**, 41 (1891).

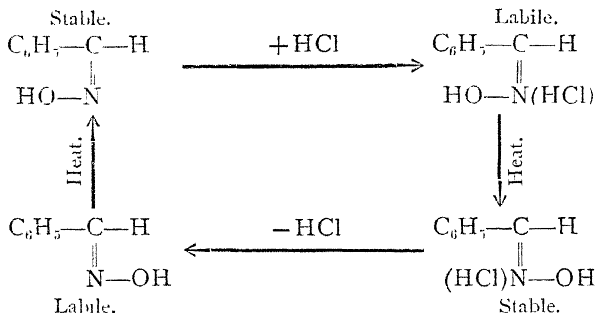
[2] Cramer, *ibid.*, **24**, 1204 (1891).

[3] Kehrmann, *Annalen*, **279**, 29 (1894); Kehrmann and Rust, *ibid.*, **303**, 24 (1898).

[4] Thiele and Pickard, *Ber.*, **31**, 1249 (1898); Biltz and Amme, *Annalen*, **321**, 1 and 7 (1902)

[5] Busch, *Ber.*, **34**, 1121 (1901).

appears that in the case of the transmutation of stereoisomeric aldoximes we must take into account two influences which appear to act in opposite directions: on the one hand, the relative stabilities of the oximes themselves, and on the other, the relative stabilities of the addition-compounds which the oximes may form with the transmuting agents used. When two stereoisomeric oximes are treated with a halogen acid, two stereoisomeric salts are formed,[1] each of which on hydrolysis will regenerate the oxime from which it was formed; but these salts have not the same relative stabilities as the oximes, and by means of the two sets of compounds it is possible to go through a cycle of changes from one isomer to the other, as is indicated in the following table :—



The addition-compounds with cuprous chloride and bromide investigated by Comstock,[2] appear to be an extreme case of this type: the anti-addition-product being so unstable that it goes over immediately into the syn-form.

§ IX. *EXPLANATIONS OF THE TRANSMUTATION OF THE STEREOISOMERS.*

Less attention has been paid to this question than to the analogous case of the transmutation of ethylene stereoisomers;

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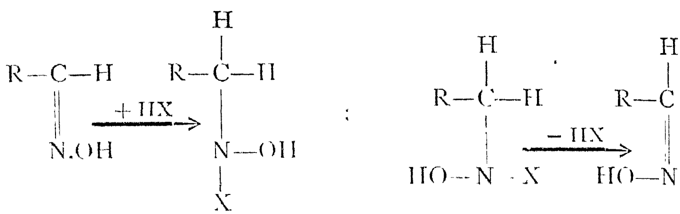
[1] Luxmoore, *Trans.*, **69**, 181 (1896)
[2] Comstock, *Amer. Chem. J.*, **19**, 485 (1897).

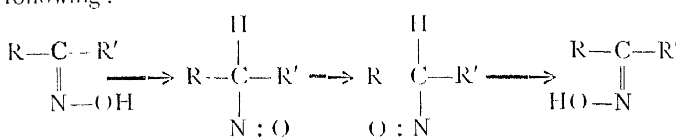
and it is therefore unnecessary to deal with the matter to any extent here.

The ideas advanced by Wislicenus with regard to the ethylene isomers can be applied almost without modification to the case of the oximes, but it cannot be said that much light is thus thrown upon the problem. If it be assumed that the stereoisomeric salts of the aldoximes correspond to the intermediate products which Wislicenus postulated, the two cases would be almost parallel; for the change from one form into the other would then be represented as follows:—



In the case of the ketoximes, a wandering similar to that supposed by Wislicenus's alternative hypothesis would be necessary.

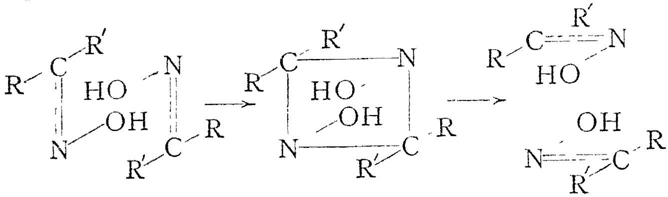
If Liebermann's idea were applied, it would result in the following:—



Skraup's theory serves as well in the case of the oximes as in that of the unsaturated acids; in the present case the necessary addition-product may be supposed to be a minute quantity of salt formed by the transmuting agent, where this is an acid.

Werner's theory, owing to its great adaptability, is probably the most satisfactory of all; but, at the same time, it should be noted that it hardly does more than restate the problem in other words.

On Stewart's hypothesis, the intermediate phase would be represented as follows :—



§ X. *THE INFLUENCE OF THE CONSTITUTION UPON THE CONFIGURATION OF STEREOISOMERIC OXIMES.*

1. The Stability Relations of the Isomers.—It has been pointed out repeatedly in the preceding pages that the configuration of an oxime can be deduced from its behaviour when undergoing certain reactions ; and so much reliance has been placed upon the results thus obtained that Hantzsch [1] has drawn up a list of radicals arranged in the order of affinity for the hydroxyl group of the oxime radical. The first members of the series have the greatest attraction for the hydroxyl group ; so that in an oxime :—

$$\begin{array}{c} R—C—R' \\ \| \\ N \\ | \\ OH \end{array}$$

if R be nearer the head of the list than R′, the hydroxyl group will lie in the syn-position to R.

(1) CH_2COOH. (2) $CH_2 : CH_2.COOH$. (3) $COOH$.
(4) C_6H_5. (5) C_6H_4X (*m* or *p*). (6) $C_6H_5.CO$.
(7) $C_6H_4X(o)$. (8) C_4H_3S, C_4H_3O. (9) C_nH_{2n+1}. (10) CH_3.

[1] Hantzsch, *Ber.*, **25**, 2164 (1892).

The following examples will make the matter clear :—

Oxime of benzoyl-acetic acid.

Very stable (only form known). Very unstable (never isolated).

Oxime of phenyl-glyoxylic acid.

Stable. Labile.

Oxime of substituted benzophenones.

Generally stable. Generally stable

The action of substituents in the benzene ring is normal. Smith[1] found that the ortho-substituents, being nearer the hydroxyl group than meta- or para-substituents, exert more influence upon it.

Oxime of acetophenone.

Very unstable (never isolated). Very stable (only form known).

It will be evident that other atoms can affect the relative stabilities of two configurations; and an explanation of certain of the facts mentioned in previous paragraphs is to be found in this way. For example, it has already been said that the oxime of phenyl-glyoxylic acid exists in one form in alkaline solution, but is transmuted into the other when the solution is acidified with hydrochloric acid. This is explained on the assumption that the attraction of a sodium atom for the carboxyl group is

[1] Smith, *Ber.*, **24**, 4057 (1891).

less than that of a hydrogen atom, so that when the hydrogen of the hydroxyl group is replaced by sodium, the compound's internal stability is altered :—

$$\begin{array}{lll} C_6H_5-& C & -COOH \\ & \| & \\ & N & -OH \end{array} \quad \underset{HCl}{\overset{NaOH}{\rightleftarrows}} \quad \begin{array}{rll} C_6H_5-& C & -COOH \\ & \| & \\ NaO- & N & \end{array}$$

2. The Progress of Certain Reactions.—It has been shown in the preceding paragraph that the relative stability of two stereoisomers can be influenced by the chemical character of the groups attached to the doubly linked carbon atom; but this influence extends much further than the mere stability of the two forms, and affects also those intramolecular reactions which are governed by the distances between the reacting atoms. In a molecule of the type X—C(NOH)—Y, the hydroxyl radical of the oxime takes up a position in space which will depend upon the relative strengths of the attractions exerted upon it by the radicals X and Y. If the attraction of X is comparatively strong, but yet so weak as to be unable to produce a change in configuration, the result might be represented graphically as below :—

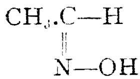
$$\begin{array}{ccc} X- & C & -Y \\ & \| & \\ & N & \\ & & \\ & & OH \end{array}$$

whereas if the attraction of Y were very strong in comparison with that of X, the configuration might be similar to the following :—

$$\begin{array}{ccc} X- & C & -Y \\ & \| & OH \\ & N & \end{array}$$

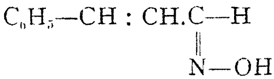
Now, in the case where Y is a hydrogen atom (*i.e.* when the compound is a synaldoxime), it is self-evident that the intramolecular elimination of water will occur most easily when the atoms are grouped as in the last example; and thus the

influence of the radical X is very great, though it is not directly concerned in the reaction. The reality of this influence becomes evident on comparing the properties of certain aldoximes in which the group R varies.



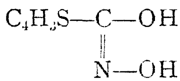
Acetaldoxime.

The acetate can not be isolated; acetic anhydride splits off water even at ordinary temperatures.



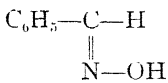
Cinnamaldoxime.

The acetate can be isolated; but it breaks down spontaneously even at ordinary temperatures.



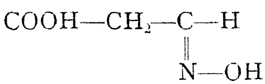
Thiophene aldoxime

The acetate can be isolated, but breaks down on standing.



Benzaldoxime.

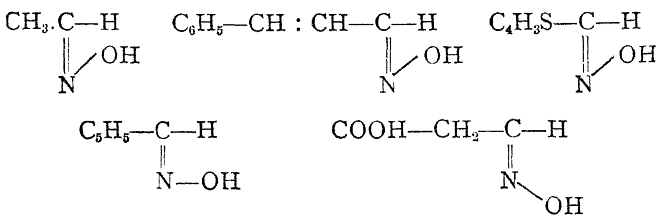
The acetate may be kept, but breaks down into the nitrile when treated with sodium carbonate solution.



Oximido-acetic acid.

The acetate is so stable that no nitrile is produced by either sodium carbonate or hydrate solution, the oxime radical being hydrolysed off.

It appears probable from the above that the configurations of these compounds can be graphically represented somewhat as follows:—



The same relations appear to hold in the case of the reaction :—

$$\begin{array}{l} R—C—COOH \\ \quad \; \| \\ \quad N—OH \end{array} = \begin{array}{l} R—C \\ \quad\;\; ||| \\ \quad\;\; N \end{array} + \begin{array}{l} CO_2 \\ \\ H_2O \end{array}$$

as can be seen from the following table :—

$\begin{array}{l} CH_3—C—COOH \\ \qquad \| \\ \quad\;\; N—OH \end{array}$ Methyl-ketoximic acid.	Breaks down with acetic anhydride without giving an acetate which can be isolated.
$\begin{array}{l} C_4H_3S—C—COOH \\ \qquad\quad \| \\ \qquad\; N—OH \end{array}$ Thionyl-ketoximic acid.	Gives an acetate which can be isolated but is unstable.
$\begin{array}{l} C_6H_5—C—COOH \\ \qquad\;\; \| \\ \qquad N—OH \end{array}$ Phenyl-ketoximic acid	Breaks down partially with acetic anhydride; gives a fairly stable acetate which decomposes with sodium carbonate solution.
$\begin{array}{l} COOH.CH_2—C—COOH \\ \qquad\qquad\quad \| \\ \qquad\qquad\; N—OH \end{array}$ Ebert's hydroximido-succinic acid.	Undecomposed by acetic anhydride.
$\begin{array}{l} H—C—COOH \\ \quad\;\, \| \\ \quad N—OH \end{array}$ Aldoximic acid	The acetate is undecomposed by soda.

Similar conclusions may be drawn from the phenomena observed during oxazolone formation.

Oxazolones are produced from β-ketoximic syn-carboxylic acids by the intramolecular liberation of water :—

$$\begin{array}{l} R—C—CH_2—COOH \\ \quad\;\, \| \\ \quad N—OH \end{array} \xrightarrow{—H_2O} \begin{array}{l} R—C——CH_2 \\ \quad\;\, \| \qquad\;\; | \\ \quad\; N \qquad CO \\ \qquad\;\; \diagdown \; \diagup \\ \qquad\quad O \end{array}$$

Now, it has already been mentioned that the radical $—CH_2.COOH$ has a very great attraction for the hydroxyl group of an oxime: and we can therefore deduce that it will require a radical R of very strong attractive power to overcome the other attraction and prevent the formation of the ring. Such a radical is only to be found in the carboxylic group. It has been shown that the ring-formation does not occur in the case of hydroximido-succinic acid so easily as in cases where R is an aromatic or aliphatic radical. As before, we can express these relations graphically :—

$$\begin{array}{l} CH_3.C—CH_2—COOH \\ \quad\ \ \Vert \quad\ \ OH \\ \quad\ \ N \end{array} \qquad\qquad \begin{array}{l} COOH—C—CH_2—COOH \\ \qquad\qquad \Vert \\ \qquad\qquad N \\ \\ \qquad\qquad\quad OH \end{array}$$

An analogous example of the influence of the constitution of certain oximes upon their configuration and reactions is to be found in the formation of oxazols in accordance with the equation :—

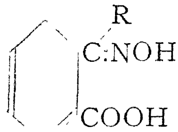
$$\begin{array}{l} R—C—CH_2—CO—X \\ \quad\ \Vert \\ \quad\ N—OH \end{array} \xrightarrow{-H_2O} \begin{array}{l} R—C—CH : C—X \\ \quad\ \Vert \qquad\qquad \vert \\ \quad\ N———O \end{array}$$

If R is an aliphatic or aromatic radical, the ring-formation is spontaneous. If R be a carboxyl group, the free oxime is stable. If R be a hydrogen atom, there is no tendency toward ring-formation, but the compounds decompose in the following manner :—

$$\begin{array}{l} H—C—CH_2—CO—X \\ \qquad \Vert \\ HO—N \end{array} = H_2O + \begin{array}{l} C—CH_2—CO—X \\ \vert\vert\vert \\ N \end{array}$$

After compounds of this configuration have been subjected to the action of transmuting agents, they form oxazols.

The same relations can be traced in the case of the oximes of those ketonic acids which have the general formula :—

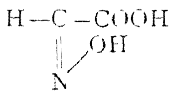


As in the last case, if R be a methyl or phenyl radical, the ring-formation is spontaneous; while if R be a hydrogen atom, the compound can exist in the free state.

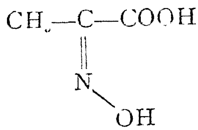
A peculiarity has been observed in the relations of the dissociation constants of the α-ketoximic acids, which may be mentioned in this place.[1] It is found that in the case of the series of acids of the general formula C_nH_{2n+1}—C(NOH)—COOH, the dissociation constants of the acids do not become continually smaller as n decreases, but decrease and increase alternately, the differences between the two numbers becoming smaller as we go further up the series. In all the compounds with which we are now concerned, hydroxyl and carboxyl radicals are in the syn-position to one another, so that the attraction of the carboxyl group for the hydroxyl group is greater than that exerted by any of the alkyl groups. But, as can be seen from the figures given below, the influence of the alkyl groups is not at all what we should expect. In the first acid, we have simply a hydrogen atom to deal with, and in this case the conductivity is high. When we replace this hydrogen atom by a methyl radical, the conductivity sinks in a marked degree. Now, it is to be expected that if we introduce an ethyl group instead of a methyl one, we should find a still further decrease in conductivity; actually, however, there is a rise instead of a fall. And when we introduce another methyl group, by changing the ethyl radical into a propyl one, we have again an anomalous result, for the conductivity is decreased. Thus with each successive step in the substitution process the affinity constant decreases on the whole, but decreases by a series of oscillations

[1] Hantzsch and Miolati, *Zeit. physikal. Chem.*, **10**, 1 (1892).

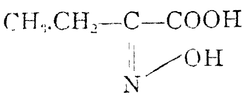
about the average fall.[4] This may be symbolized by the formulæ below :—



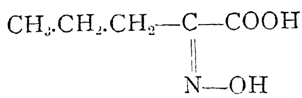
K = 0·0995



K = 0·0514



K = 0·0830.



K = 0·0685.

§ XI SOME UNEXPLAINED CASES OF ISOMERISM IN THE CARBON-NITROGEN COMPOUNDS.

Lossen,[1] Werner,[2] and Subak[3] have found that methylbenzhydroximic acid :—

$$\begin{array}{l} C_6H_5-\underset{\displaystyle \| \atop \displaystyle N-OH}{C}-O-CH_3 \end{array}$$

exists in three different modifications, though only two are provided for by the theory. The syn-form has a melting-point of 44° C., while the anti-form melts at 64° C. The third isomer, which is easily obtained from the anti-form, has a melting-point of 101° C. Both the 64° C. and the 101° C. substance give the same benzoyl-derivative; and the molecular weight of the 101° C.

[4] Compare the somewhat analogous case of the melting-points of the cyclic dicarboxylic acids on p. 150. It should be noted, however, that the deduction drawn by Hantzsch is not the only possible one; for if the conductivity of hydroximido-propionic acid be abnormal, the three other merely form a descending series of no particular interest.

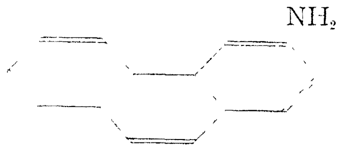
[1] Lossen, *Annalen*, **281**, 199 (1894); **282**, 226 (1894).

[2] Werner, *ibid.*, **29**, 1150 (1896).

[3] Subak, *ibid.*, **29**, 1153 (1896).

modification is simple. Werner attributes the existence of the third isomer to some kind of physical isomerism.

Another case, though not quite of the same character, has been observed by Werner and Kuntz,[1] who found that 3-phenanthrylamine exists in two forms, one of which melts at 143° C., and the other, obtained from the acetyl-derivative of the first, at 87·5° C. On acetylation, both compounds yield the same



derivative. Each substance gives a series of crystalline salts, which on decomposition regenerate that isomer from which they were produced.

[1] Werner and Kuntz, *Ber.*, **34**, 2325 (1901).

CHAPTER IV.

STEREOISOMERISM IN NITROGEN COMPOUNDS.

§ I. *HISTORICAL.*

It is unnecessary to deal with the history of the diazo-compounds previous to 1894, as up to that time no facts of stereochemical interest were known. In that year, however, Schraube[1] observed that when normal potassium benzene diazotate, $C_6H_5N_2OK$, was treated with alkali it was converted into a new isomeric compound, potassium benzene isodiazotate, which was distinguished from the original substance by having no power of coupling with β-naphthol to form azo-dyes. Bamberger[2] shortly after this discovered the naphthalene isodiazotate of potassium, though he was unable to isolate the normal compound.

The constitution of these bodies was determined in the following manner. It was found that when the iso-diazo potassium salts were treated with methyl iodide they yielded nitrosamines; *e.g.* the potassium salt of isodiazobenzene, $C_6H_5N_2OK$, produces methyl-phenyl-nitrosamine, $C_6H_5.N(CH_3).NO$. From this reaction Bamberger and others concluded that the iso-diazo salts had the formula $C_6H_5.NK.NO$. Hantzsch[3] brought forward some evidence against this hypothesis, and, instead of it, put forward the suggestion that the two diazo salts were structurally identical but stereoisomeric compounds. The formation of the nitrosamine he was able to account for by simple

[1] Schraube, *Ber.*, **27**, 514 (1894).
[2] Bamberger, *ibid.*, **27**, 679 (1894).
[3] Hantzsch, *ibid.*, **27**, 1701 (1894).

tautomerism, the one tautomeric form being $C_6H_5.N:N.OK$, and the other being $C_6H_5.NK.NO$. The case is somewhat similar to that of the oxime derivatives. Later work has shown the probability of Hantzsch's view, for new series of isomeric compounds have been discovered in which the nitrosamine form would be most unlikely to exist; for example, the diazo-sulphonates, $R.N:N.SO_3K$, and the diazo-cyanides, $R.N:N.CN$.

§ II. *THE STRUCTURAL IDENTITY OF THE ISOMERIC DIAZO-COMPOUNDS.*[1]

It would be useless to enter into a detailed discussion of the reasons which led to the abandonment of formulæ * such as:—

$$\begin{array}{l}Ar\text{—}N\text{—}N:O\\ \qquad\ |\\ \qquad X\end{array}\qquad\qquad \begin{array}{c}Ar\text{—}N\text{——}N\text{—}X\\ \qquad\ \ \diagdown\ \diagup\\ \qquad\ \ O\end{array}\qquad\qquad \begin{array}{l}Ar\text{—}N:N\text{—}X\\ \qquad\ \|\\ \qquad O\end{array}$$

since such discussions do not lie within the province of a book upon stereochemistry. There is, however, one formula which must be dealt with, as it is essential from the stereochemical point of view to make clear its relations with the formula suggested by Hantzsch.

Blomstrand, Erlenmeyer sen., and Strecker suggested for the diazo-compounds the formula:—

$$\begin{array}{l}Ar\text{—}N\text{—}X\\ \qquad\ |||\\ \qquad\ N\end{array}$$

which, from its resemblance to an ammonium salt formula, was called the diazonium formula. This formula fell out of use, but was revived and utilised to express the second isomeric diazo-compound:—

$$\begin{array}{l}Ar\text{—}N\text{—}X\\ \qquad\ |||\\ \qquad\ N\end{array}\qquad\qquad\qquad Ar\text{—}N:N\text{—}X$$

Normal form. Iso-form.

* Ar represents an aromatic radical in these formulæ.

[1] Reference may be made to Hantzsch: *Die Diazo-verbindungen.*

Hantzsch investigated the matter, and showed that the acid salts of diazo-benzene certainly agreed very closely in properties with the ammonium salts; but from this very resemblance he concluded that the diazonium formula could not represent the normal diazo-compounds, since there are no ammonium compounds of the type $R_4N.OX$ or $R_4N.SO_3X$, and the ammonium cyanides $R_4N.CN$ have properties differing entirely from those of the indifferent normal diazo-cyanides. Hantzsch therefore regarded the diazonium salts as belonging to a class by themselves, apart from the stereoisomeric diazo-compounds of the formula Ar—N : N—X. As this point is important, we shall deal with it in detail.

In the first place, it must be shown that the normal diazotates cannot be expressed by the diazonium formula. If they could be, their structure would be:—

$$\begin{array}{l} Ar{-}\overset{}{N}{-}OX \\ \Vert\!| \\ N \end{array}$$

where X is a metallic atom. But the diazo-hydrates are strongly basic compounds, and it is not at all probable that such substances in aqueous solution would react with alkalis to form stable salts. It has been proved, however, that the diazotates are really salts, which may be derived from a hydrate $Ar.N_2.OH$, whose acidic properties, though weak, are undoubted. The nearest analogy appears to be the acidic properties of the oximes. It has been suggested that the diazonium radical resembles those metals the hydroxides of which have the property of reacting either as a base or as an acid. The diazonium group, however, differs from these amphoteric electrolytes, for when it displays acid properties they are much stronger than those of tin, lead, aluminium, or zinc; and when it shows negative properties it surpasses these elements in this case also. Evidently the strongly positive diazonium ion:—

$$\begin{array}{l} Ar{-}N^{\circ} \\ \Vert\!| \\ N \end{array}$$

cannot become strongly negative by the simple addition of oxygen :—

$$\begin{array}{ccccc} \mathrm{Ar} & - & \mathrm{N} & - & \mathrm{O}' \\ & & \vert\vert\vert & & \\ & & \mathrm{N} & & \end{array}$$

The diazonium formula is therefore unsuitable for diazotates.

We must now show that the normal diazo-sulphonates cannot be expressed either as diazonium-sulphonates or diazonium sulphites :—

$$\begin{array}{ccccc} \mathrm{Ar} & - & \mathrm{N} & - & \mathrm{SO_3X} \\ & & \vert\vert\vert & & \\ & & \mathrm{N} & & \end{array} \qquad\qquad \begin{array}{ccccc} \mathrm{Ar} & - & \mathrm{N} & - & \mathrm{O.SO_2X} \\ & & \vert\vert\vert & & \\ & & \mathrm{N} & & \end{array}$$

From analogy with the ammonium salts, it would be quite out of the question to suppose that diazonium could form sulphonates. The sulphonate formula may therefore be excluded from the discussion, and we are left with the sulphite formula. This also can be shown to be untenable, for in aqueous solution a diazonium sulphite would form three ions,

$$\begin{array}{ccc} \mathrm{Ar} & - & \mathrm{N}^{\circ} \\ & & \vert\vert\vert \\ & & \mathrm{N} \end{array}, \ \mathrm{K}^{\circ}, \text{ and } \mathrm{SO_3}''.$$

Actually, however, the sulphonates give rise to only two ions, $\mathrm{Ar{-}N_2{-}SO_3}'$ and K°. Further, so long as their ions remain intact, *e.g.* in alkaline solution, the sulphonates do not give the reactions either of diazonium salts or of sulphites. Finally, since the diazonium ion is colourless, all diazonium salts with colourless anions should be colourless, while actually the labile diazo-sulphonates are coloured.

Lastly, we must show that the normal diazo-cyanides cannot have the diazonium formula :—

$$\begin{array}{ccccc} \mathrm{Ar} & - & \mathrm{N} & - & \mathrm{CN} \\ & & \vert\vert\vert & & \\ & & \mathrm{N} & & \end{array}$$

A true diazonium cyanide should resemble ammonium or potassium cyanide in properties. The anhydrous normal diazo-cyanides, however, differ from ordinary cyanides in most properties. They are only slightly soluble in water, but are soluble in most

organic liquids in which the alkali cyanides are insoluble. Unlike the alkali cyanides, they are strongly coloured. And, finally, they are so stable in presence of acids that many of them under these conditions evolve no hydrocyanic acid. It is evident that the two classes of substances differ too much to be of a similar nature: and it seems certain that the diazo-cyanides are not salts, but indifferent organic substances. A complete proof of the correctness of Hantzsch's view was given by the discovery, in the case of anisyl diazo-cyanide, $CH_3O.C_6H_4.N_2.CN$, of all three forms—two isomeric syn- and anti-cyanides, and the diazonium cyanide.

Having shown that the isomerism of the diazo-compounds cannot be expressed by the diazonium and other formulæ, we must now prove that the compounds are stereoisomeric; and in order to do this, we must show that the structural formulæ of the two isomeric forms are identical. The following *resumé* of their properties will show some of the evidence in favour of this view.

The normal and the iso-diazotates are colourless salts, both of which in aqueous solution yield the isomeric anion $Ar—N_2.O'$. Neither series depolarizes a hydrogen electrode.

The normal and iso-diazo-sulphonates are coloured salts both of which in aqueous solution yield two ions, the anions being isomeric and coloured.

The normal and iso-diazo-cyanides are coloured, indifferent substances, which dissolve unchanged, have a low melting-point, and behave in every way like true organic compounds.

All changes which take place in the diazo-complex seem to follow the same course in the normal and in the iso-diazo series. Both normal and iso-diazotates are easily reduced to hydrazines; benzoyl chloride converts both into nitroso-anilides, and by oxidation both yield nitraminic salts of the type $Ar.N_2O.OX$. The same is true for the isomeric diazo-sulphonates. Further, under exactly the same conditions in each case, the two series of diazo-cyanides are converted into diazo-amides, diazo-imino-ethers, etc. It has also been shown that, without undergoing any previous isomeric change, the compounds of each series unite with benzene sulphinic acid to form addition-compounds analogous to hydrazo-benzene:—

$$\mathrm{Ar{-}N:N{-}CN + C_6H_5.SO_2H} = \begin{array}{c}\mathrm{Ar}\diagdown \qquad \diagup\mathrm{CN} \\ \quad\mathrm{N{-}N} \\ \mathrm{H}\diagup \qquad \diagdown\mathrm{SO_2C_6H_5}\end{array}$$

Many other similarities of chemical behaviour could be adduced, but sufficient has been said to show that the structural nature of the two isomeric series is probably the same. But since the isomerism is similar in the cases of the diazotates, the diazo-cyanides and the diazo-sulphonates, it is evident that the origin of the isomerism is to be sought in the complex $\mathrm{Ar{-}N_2{-}}$, and not in the radicals attached to this nucleus.

Now, if we consider the possible grouping of the atoms within the radical $\mathrm{Ar{-}N_2{-}}$, it is evident that we need only take into account the following three:—

$$(1)\ \mathrm{Ar{-}N{=}N{-}X} \qquad (2)\ \begin{array}{c}\mathrm{Ar{-}N{-}X} \\ \equiv \\ \mathrm{N}\end{array} \qquad (3)\ \mathrm{Ar{-}N{\equiv}N{-}X}$$

Since the behaviour of the iso-diazo-compounds shows them to have the formula (1), we need only consider the other two for the normal diazo-compounds. It has, however, already been shown that these have not the structure (2); and the formula (3) suffers under almost exactly the same disadvantages as (2). We are therefore left with no alternative but to assume that the formula (1) expresses the behaviour of the normal diazo-compounds also. But if the compounds be structurally identical, their isomerism must be of a stereochemical nature.

§ III. *THEORETICAL.*

According to Hantzsch, the compounds of the type $\mathrm{Ar.N_2.X}$ can exist in two stereoisomeric forms, which he expresses in the following way:—

$$\begin{array}{c}\mathrm{Ar{-}N} \\ \quad\| \\ \mathrm{X{-}N}\end{array} \qquad\qquad \begin{array}{l}\mathrm{Ar{-}N} \\ \qquad\| \\ \qquad\mathrm{N{-}X}\end{array}$$

Labile syn-diazo-compound. Stable anti-diazo-compound.

organic liquids in which the alkali cyanides are insoluble. Unlike the alkali cyanides, they are strongly coloured. And, finally, they are so stable in presence of acids that many of them under these conditions evolve no hydrocyanic acid. It is evident that the two classes of substances differ too much to be of a similar nature: and it seems certain that the diazo-cyanides are not salts, but indifferent organic substances. A complete proof of the correctness of Hantzsch's view was given by the discovery, in the case of anisyl diazo-cyanide, $CH_3O.C_6H_4.N_2.CN$, of all three forms—two isomeric syn- and anti-cyanides, and the diazonium cyanide.

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Many other similarities of chemical behaviour could be adduced, but sufficient has been said to show that the structural nature of the two isomeric series is probably the same. But since the isomerism is similar in the cases of the diazotates, the diazo-cyanides and the diazo-sulphonates, it is evident that the origin of the isomerism is to be sought in the complex $\mathrm{Ar{-}N_2{-}}$, and not in the radicals attached to this nucleus.

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Labile syn-diazo-compound. Stable anti-diazo-compound.

where X may be —CN,—SO_3M, or —OM. This is merely a further step in advance from the Hantzsch-Werner theory of the oximes, just as that theory was in its turn an advance along the lines laid down by van't Hoff and Le Bel. The three cases may be given here for the sake of comparison—

I. In carbon compounds :—

$$\begin{array}{c} R—C—H \\ \| \\ R'—C—H \end{array} \qquad\qquad \begin{array}{c} R—C—H \\ \| \\ H—C—R' \end{array}$$

Cis-form. Trans-form.

II. In carbon-nitrogen compounds :—

$$\begin{array}{c} R—C—H \\ \| \\ R'—N \end{array} \qquad\qquad \begin{array}{c} R—C—H \\ \| \\ N—R' \end{array}$$

Syn-form. Anti-form.

III. In nitrogen compounds :—

$$\begin{array}{c} R—N \\ \| \\ R'—N \end{array} \qquad\qquad \begin{array}{c} R—N \\ \| \\ N—R' \end{array}$$

Syn-form. Anti-form.

The syn-compounds correspond to the normal diazo-compounds, while the anti-form represents what were previously called iso-diazo-compounds. For the sake of clearness, the tetrahedron may be drawn just as in the case of the carbon atom, thus :—

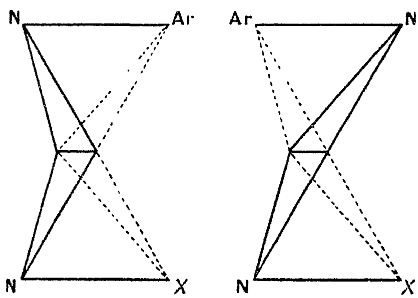


FIG. 43.

§ IV. *THE METHODS OF FORMATION OF THE ISOMERIC DIAZO-COMPOUNDS.*

When alkali hydroxides, silver oxide, potassium sulphite, or potassium cyanide are allowed to act upon diazonium salts, syn-diazo-compounds are formed. Nothing appears to be known with regard to the mechanism of this reaction, which can be expressed by the following equation :—

$$\begin{array}{c} Ar—N—X \\ \quad\ \ \vert\vert\vert \\ \quad\ \ N \end{array} + KOH = \begin{array}{r} Ar—N \\ \Vert \\ HO—N \end{array} + KX$$

Syn-compounds are obtained by other reactions as well. For example, when a hydrazine derivative is oxidised with mercuric oxide to a diazo-compound :—

$$Ar—NH—NH—R + O = Ar—N : N—R + H_2O$$

a syn-compound is first produced. In the ordinary diazotisation of an aromatic amine, the first substance produced is the syn-variety.

The trans-forms are obtained from the cis-forms by intramolecular change; the method employed will be described in the section dealing with the transmutation of the isomers.

§ V. *THE DETERMINATION OF THE CONFIGURATION OF THE STEREOISOMERIC DIAZO-COMPOUNDS.*

There are three methods by which the configuration of a given diazo-compound may be ascertained: by a difference in chemical activity between the two isomers; by intramolecular decomposition; and by intramolecular ring-formation. We shall deal with these in turn.

It was pointed out in the case of the ethylene stereoisomers, that the labile form possessed a greater energy content than the stable form: and if this, by analogy, be supposed to hold good in the case of the diazo-compounds, we should expect to find differences in chemical activity between the two

isomeric forms; accordingly, compounds possessing the less symmetrical syn-formula would be expected to fall into line with the labile stereoisomers of other types which are also unsymmetrical in configuration. This view can be supported by a considerable amount of evidence. For example, the syn-compounds are more explosive than the anti-isomers; they are more easily reduced or oxidized; and are more easily converted into nitroso-amides. The most striking difference in chemical properties is to be found in the case of the reaction between a diazo-compound and β-naphthol; for in this case the difference between the coupling capacities of the two series is very strongly marked. The syn-compounds couple immediately, in large quantity; while the yield from the anti-isomer is comparatively small. Differences between the two compounds are also observed in the case of water of crystallization, the syn-compound in some cases crystallizing with one molecule of water while the anti-form is anhydrous.

The physical properties of the two isomers differ considerably from one another. The unstable forms have a greater solubility and lower melting-point than the stable variety, a difference which recalls the case of the ethylene isomers.

It has already been repeatedly pointed out that, from the stereochemical point of view, an intramolecular reaction will take place most easily when the two groups concerned lie near to each other in space. Now, it is found that derivatives of the unstable diazo-series decompose much more readily than the corresponding stable isomers. From this it is deduced that the groups concerned in the decomposition lie much nearer to one another in the syn-compounds than they do in the anti-forms.[1] For instance, normal (syn) diazo-compounds decompose directly according to the equation :—

$$\begin{array}{c} \mathrm{Ar{-}N} \\ \quad\ \ \| \\ \mathrm{X{-}N} \end{array} \longrightarrow \begin{array}{c} \mathrm{Ar} \\ | \\ \mathrm{X} \end{array} + \begin{array}{c} \mathrm{N} \\ ||| \\ \mathrm{N} \end{array}$$

Again, the syn-diazotate of sulphanilic acid decomposes almost

[1] Angeli, *Gazzetta*, **24**, II., 369 (1894).

quantitatively at ordinary temperatures into potassium phenol-sulphonate and nitrogen :—

$$\begin{array}{r} SO_3K.C_6H_4.N \\ \| \\ HO\text{—}N \end{array} \longrightarrow \begin{array}{r} SO_3K.C_6H_4 \\ | \\ HO \end{array} + \begin{array}{c} N \\ ||| \\ N \end{array}$$

And syn-diazo-cyanides in presence of copper dust are decomposed into nitrogen and a nitrile :—

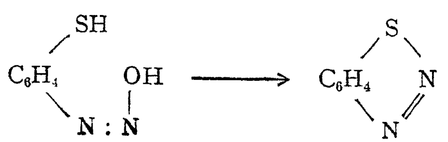
$$\begin{array}{r} C_6H_5\text{—}N \\ \| \\ CN.N \end{array} \longrightarrow \begin{array}{c} C_6H_5 \\ | \\ CN \end{array} + \begin{array}{c} N \\ ||| \\ N \end{array}$$

This appears to be analogous to the decomposition of the syn-oximes into nitriles and water :—

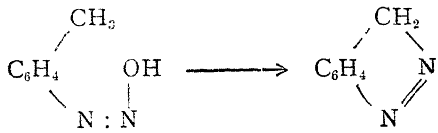
$$\begin{array}{l} H\text{——}C\text{—}C_6H_5 \\ \quad\quad\quad \| \\ HO\text{—}N \end{array} \longrightarrow \begin{array}{c} H \\ | \\ HO \end{array} + \begin{array}{l} C\text{—}C_6H_5 \\ ||| \\ N \end{array}$$

On the other hand, when the anti-diazo-compounds are used, these reactions either do not occur, or at the best are very slow in their progress.

The third method, from intramolecular ring-formation, depends upon the same principle. In the case of the anhydride formation of maleic and fumaric acid, we have already had an example of a difference between two isomers, as regards the formation of a ring within the molecule. Intramolecular ring-formation is a common reaction with the diazo-compounds, and it appears that the syn-compounds are those which form the rings most easily. Two examples of the production of cyclic compounds may be given. The hydrate of syn-*o*-diazo-thiophenol loses water spontaneously, and is converted into benzo-thiodiazol :—



And a similar loss of water takes place in the case of ortho-methylated diazo-hydrates, leading to indazol formation :—



§ VI. *THE TRANSFORMATION OF THE ISOMERIC DIAZO-COMPOUNDS INTO ONE ANOTHER AND INTO NITROSAMINES.*

1. Transmutation of Syn- into Anti-compounds.—A direct conversion of the syn-isomer into the corresponding trans-compound can easily be brought about. In the case of the diazo-hydrates, it can be produced by solution in aqueous alkali; the syn-diazo-sulphonates can be changed into the anti-configuration by the same method; while the diazo-cyanides require an alcoholic solution. In some cases, however, these methods fail, and it is then necessary to form the addition-compound with benzene sulphinic acid and pass over into the anti-compound by loss of the sulphinic acid :—

$$\begin{array}{l} \text{Ar}-\text{N} \\ \quad \| \\ \text{X}-\text{N} \end{array} + C_6H_5SO_2H \longrightarrow \begin{array}{l} \text{Ar}-\text{N}-\text{H} \\ \qquad | \\ \text{X}-\text{N}-C_6H_5SO_2H \end{array} \xrightarrow[\text{or KOH}]{\text{HCl}} \begin{array}{l} \text{Ar}-\text{N} \\ \qquad \| \\ \qquad \text{N}-\text{X} \end{array} + C_6H_5SO_2H$$

No means are at present known by which compounds of the anti-series can be directly converted into syn-derivatives; but an indirect method is sometimes used. When an anti-diazotate is treated with an acid chloride, it gives rise to an acyl-nitrosamine,[1] which on treatment with potash produces the syn-form.

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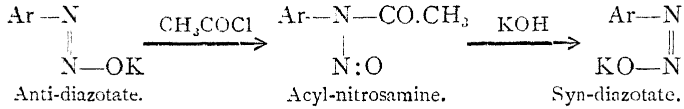
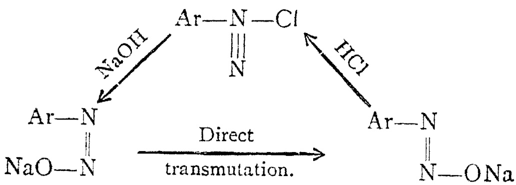
[1] Von Pechmann, *Ber.*, **27**, 656 ; Bamberger, *ibid.*, 915 (1894).

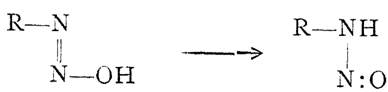


Since anti-compounds can be converted into isomeric diazonium bodies by means of hydrochloric acid, and the diazonium derivative in turn can be changed into a syn-compound by the action of sodium hydrate, a complete series of changes can be brought about which may be represented by the following scheme :—



2. **Conversion of Syn-diazo- into Diazonium Compounds, and vice versâ.**—This change is never found to be complete; but an equilibrium mixture of the two isomers is always formed. The change of diazonium to diazo-compound is brought about by the action of alkalis, potassium cyanide, or potassium sulphite upon the diazonium salt; while the reverse change takes place in the presence of acids.

3. **Change of Anti-diazo-compounds into Nitrosamines.**—The syn-diazo-compounds show a marked resemblance to the diazonium salts; while the anti-diazo-compounds approach more to the primary nitrosamine type; this is especially true of the anti-diazo-hydrates. These compounds are obtained by the action of acids upon their salts. When generated, they are weak acids; but they soon lose this property, for, owing to their very great instability, they are rapidly converted into the isomeric nitrosamines :—



Both the nitrosamine and the anti-diazo-compound can be converted into the corresponding diazonium salt by treating their aqueous solutions with acids.

§ VII. *THE INFLUENCE OF THEIR CONSTITUTION UPON THE CONFIGURATION OF STEREOISOMERIC DIAZO-COMPOUNDS.*

Hantzsch makes the following generalisations upon this question :—(1) In the relations between diazonium and diazo-compounds, if the benzene nucleus be made more positive in character by the introduction of alkyl radicals, the diazonium type is rendered more stable; while the converse is true if the benzene group be made more negative in character by the substitution of halogen atoms for hydrogen. For example, trimethyl-diazo-benzene bromide, $(CH_3)_3.C_6H_2.N:N.Br$, is very slightly explosive, and has but little colour; while tribromo-diazo-benzene bromide, $Br_3.C_6H_2.N:N.Br$, is extremely explosive and intensely coloured. (2) In the relations between syn- and anti-diazo-compounds, the influence of substituents in the benzene ring can be traced, though it is less marked than in the previous case. Its greatest effect is shown in the transmutation of the isomers. In the case of the diazotates, methyl substituents seem to hinder the transmutation, while halogen atoms facilitate it. For instance, the transmutation of trimethyl-benzene-syn-diazotate, $(CH_3)_3.C_6H_2.N:N.OX$, is very difficult to bring about; benzene-syn-diazotate, $C_6H_5.N:N.OX$, is much easier to transmute, as it changes at a temperature above 100° C.; while the *p*-bromo-derivative, $Br.C_6H_4.N:N.OX$, is changed by mere boiling with alcohol. In the case of the diazo-sulphonates these conditions are reversed, for in their case halogens hinder the change, while alkyl groups facilitate it. The same is true for the diazo-cyanides. In all three cases the nitro-group facilitates the transmutation. (3) In the relations between anti-diazo-hydrates and primary nitrosamines, the presence of halogen atoms in the benzene ring appears to favour the nitrosamine formation.

§ VIII. *DIAZO-COMPOUNDS WHICH DO NOT EXHIBIT STEREOISOMERISM.*

In the class of the diazo-compounds, by far the greater number of substances have as yet been prepared in one form only. This, in most cases, is the anti-configuration. It appears probable that in these compounds the syn-form is extremely labile, and is thus converted into the trans-form before it is possible to isolate it. Examples of this type are tri-bromo-benzene-diazotates, all nitro-benzene-diazotates, all diazo-phenol-sulphonates, and all diazo-cyanides. On the other hand, some cases are known in which the only existing form belongs to the syn-series. For instance, naphthalene diazo-sulphonates, $C_{10}H_7.N:N.SO_3X$, and pseudo-cumol diazo-cyanide, $(CH_3)_3C_6H_2.N:N.CN$, exist only in one form, and show all the properties of syn-compounds.

§ IX *THE CONFIGURATION OF NON-AROMATIC DIAZO-COMPOUNDS.*

According to Hantzsch, the open-chain azo- or diazo-compounds, such as azo-dicarboxylic ester, $COOEt—N:N—COOEt$, and potassium azomethane sulphonate, $CH_3—N:N—SO_3K$, from their stability must be classed as anti-compounds. The cyclic fatty diazo-compounds, such as diazo-methane, $CH_2\begin{matrix} \diagup N \\ \| \\ \diagdown N \end{matrix}$, or diazo-acetic ester, $\begin{matrix} N\diagdown \\ \| \\ N\diagup \end{matrix}CH.COOEt$, from their methods of formation and decomposition, must be considered as internal anhydrides of syn-diazo-hydrates.

$$\begin{matrix} N.CH_2.COOEt \\ \| \\ N.OH \end{matrix} \longrightarrow \begin{matrix} N\diagdown \\ \| \\ N\diagup \end{matrix}CH.COOEt$$

Hantzsch[1] has also suggested that nitramide and hyponitrous

[1] Hantzsch, *Annalen*, **292**, 340 (1896).

acid are really structurally identical; and that they owe their isomerism to space differences. He formulates them thus.—

$$\begin{array}{cc} \text{HO.N} & \text{HO N} \\ \| & \| \\ \text{HO.N} & \text{N.OH} \end{array}$$

Syn-diazohydrate (Nitramide.) — Anti-diazohydrate. (Hyponitrous acid.)

§ X. *OTHER CASES OF STEREOISOMERISM IN TRIVALENT NITROGEN COMPOUNDS.*

We must now consider the evidence in favour of the existence of stereoisomeric compounds of the type N*abc*. Miller and Plöchl,[1] by the action of asymmetric xylidine upon acid aldehydes in alcoholic solution, prepared a mixture of two isomeric substances, both of which gave the following reactions. They gave the tests for an aldehyde group; they gave the same benzoyl derivative; they both condensed with *m*-xylidine to give the same product, whose formula was supposed to be :—

$$\begin{array}{l} (CH_3)_2.C_6H_3.NH.CH.CH_2 \\ \qquad\qquad\qquad\quad | \\ (CH_3)_2.C_6H_3.N:CH.CH_2 \end{array}$$

Finally, it was found that they differed only in solubility and melting-point, and could be converted into one another easily These facts can best be expressed in the formula :—

$$\begin{array}{l} (CH_3)_2.C_6H_3.NH.CH.CH_3 \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad\qquad\quad CH_2 \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad\qquad\quad CHO \end{array}$$

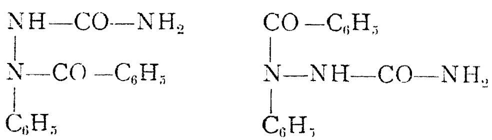
Miller and Plochl, in order to explain this case of isomerism, postulated that the three valencies of the nitrogen atom are so arranged in space that the compound N*abc* can exist in two forms, which may be expressed by :—

[1] Miller and Plöchl, *Ber.*, **25**, 2025 (1892); **27**, 1281 (1894); **29**, 1462 (1896).

Willgerodt found that when dinitro-chlorobenzene was allowed to act upon phenylhydrazine, the result was a mixture of two products, one being an amorphous powder which was readily transformed into the other isomer, a crystalline substance. A similar isomerism was noticed when either α- or β-naphthylhydrazine was substituted for phenylhydrazine. An explanation was put forward, based upon the idea that the nitrogen valencies were distributed in space in the manner indicated above, the two isomeric forms being represented by the formulæ :—

This implies that the rotation of the two nitrogen atoms about their common axis has been prevented in this case—a view which cannot be brought into harmony with our present knowledge of the behaviour of two atoms united by a single bond.

Young and Annable,[2] by the action of benzoyl chloride upon phenyl-semicarbazide, prepared two isomeric products of the same general formula; they attributed the isomerism to stereochemical differences expressed in the formulæ—



The work of Widman,[3] and of Michaelis and Schmidt[4] should also be consulted on this point.

[1] Willgerodt, *J. pr. Chem.*, [2] **37**, 449 (1888); Willgerodt and Schultz, *ibid.*, **43**, 177 (1891).

[2] Young and Annable, *Trans.*, **71**, 204 (1897)

[3] Widman, *Ber.*, **26**, 948 (1893).

[4] Michaelis and Schmidt, *ibid.*, **20**, 1713 (1887)

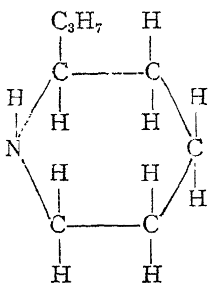
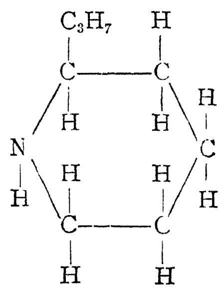
Quite recently, Willstatter and Benz[1] observed a case of isomerism in the azo-series. They found that if *p*-azophenol were oxidised, the resulting quinone-azine yielded on reduction a new azo-phenol. They advanced the explanation that the two bodies were stereoisomers of the configurations :—

$$\begin{array}{lr} HO.C_6H_4\text{—}N & \\ \quad\quad\quad\quad\ \ \| & \\ \quad\quad\quad\quad\ \ N\text{—}C_6H_4.OH \end{array} \qquad \begin{array}{l} N\text{—}C_6H_4.OH \\ \| \\ N\text{—}C_6H_4.OH \end{array}$$

It is not yet proved that this is the case.

We must now turn to those compounds in which the nitrogen atom is a member of a ring, so that two of its valencies are maintained in one plane. This case, being parallel to that of the oximes, seems to offer more chance of the occurrence of stereoisomerism than is given by the cases we have just been considering.

Ladenburg[2] found that by distilling coniine hydrochloride with zinc dust and a little water, he was able to produce a new isomeric compound, which has been called iso-coniine. This new isomer differs from coniine itself only in its optical rotatory power, and the solubility of its platinichloride in alcohol and ether. Ladenburg attributes the isomerism to steric causes, supposing it to be a kind of cis-trans isomerism expressible in the two formulæ :—

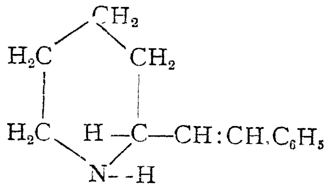
 

In one of the figures, the hydrogen atom attached to the nitrogen lies on the same side of the ring as the isopropyl radical; while

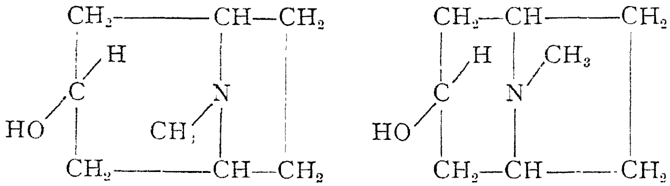
[1] Willstatter and Benz, *Ber.*, **39**, 3492 (1906).

[2] Ladenburg, *ibid.*, **26**, 854 (1893); compare *ibid.*, **34**, 3416 (1901).

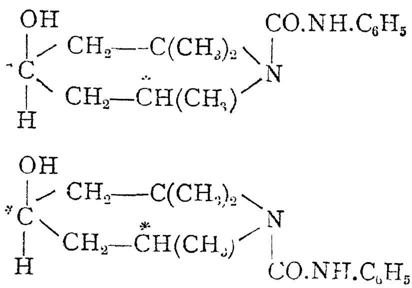
in the second figure the two lie on opposite sides of the ring. A similar case was observed by Ladenburg[1] in stilbazoline :—



for this substance, on heating in a sealed tube to 300° C., gave an isomeric compound, isostilbazoline, of different rotatory power. Here again the solubilities of the two isomers are different. The same explanation has been applied to the case of tropine and ψ-tropine; the methyl group being in one case supposed to be on the same side of the molecule as the hydroxyl group, and in the other case to be on the opposite side of the molecule :—

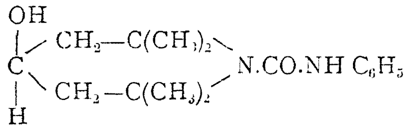


Groschuff[2] explains the occurrence of two forms of the following phenyl-isocyanate derivative of α-vinyldiacetone-alkamine in like manner :—



[1] Ladenburg, *Ber.*, **36**, 3694 (1903).
[2] Groschuff, *ibid.*, **34**, 2974 (1904).

It might be suggested that this isomerism was due to the presence in the ring of the two asymmetric carbon atoms marked with asterisks. Since, however, the same isomerism occurs in the triacetone-alkamine :—



in which there is no asymmetric carbon atom, it seems that the cis-trans explanation is the only adequate one.

§ XI. *STEREOISOMERISM IN INACTIVE COMPOUNDS OF PENTAVALENT NITROGEN.*

In the series of salts of pentavalent nitrogen, several cases are known in which inactive isomeric salts of different crystalline form exist. Le Bel discovered several such instances, but he has recently[1] announced that he considers them to be merely cases of dimorphism, and not of stereo-isomerism.

Schryver[2] obtained two platinum salts of methyl-diethyl-isoamyl-ammonium chloride, which differed from one another in crystalline character.

Evans,[3] by the action of propyl iodide on ethyl-piperidine, or of ethyl iodide on propyl-piperidine, produced a mixture of hemihedral crystals of the monosymmetrical system. Neither of the forms was optically active.

Wedekind found several cases of what he supposed to be inactive stereo-isomeric substances; but, on further investigation,[4] these have been proved to be either structure isomers or not isomeric compounds at all.

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[1] Le Bel, *J. Chim. phys.*, **2**, 340 (1904)
[2] Schryver, *Proc.*, **7**, 39 (1891).
[3] Evans, *Trans.*, **71**, 522 (1897)
[4] Jones, *ibid.*, **87**, 1721 (1905)

Aschan[1] prepared two derivatives of ethylene-dipiperidine and methyl iodide which appeared to be dimorphous. Later work has shown that they were the same substance.

The evidence in this question, therefore, is mostly negative; and it seems not unfair to conclude that the cases which have been observed are cases of dimorphism rather than of stereo-isomerism.

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[1] Aschan, *Ber.*, **32**, 988 (1899).

CHAPTER V.

STEREOISOMERISM IN COBALT COMPOUNDS.

§ I. *GENERAL.*

IN the remaining chapters of this section the theory put forward by Werner[1] will be briefly treated. It seems possible only to sketch the outlines of his work, as up to the present there does not appear to be a sufficient accumulation of material to allow more than this to be done.

In order to explain the formation of molecular compounds from simple salts, Werner has put forward the hypothesis that there are really two sets of valencies concerned in the formation of a molecular compound, *i.e.* a double salt. Those valencies which are utilised in the structure of simple salts he designates *Principal Valencies*, while those which are brought into play by the formation of double salts are termed by him *Auxiliary Valencies*. It must not be supposed that these two classes differ in any *essential* quality; they are merely different in degree, just as a yard and an inch differ from one another.

§ II. *NOMENCLATURE.*

Werner[2] has suggested the following system of nomenclature for the stereo-isomeric cobalt salts. The name of any given compound is made up of the names of the atoms and

---

[1] Werner, *Annalen*, **322**, 261 (1902). An historical account of this work has been given by Werner (*Ber.*, **40**, 15 (1907)). Full references are to be found in that paper. See also *Annalen*, **351**, 65 (1907).

[2] Werner, *Zeit. anorgan. Chem.*, **14**, 21 (1897).

atomic groups of which the molecule is composed. All atoms or radicals which, being directly united to the metallic atom, form with it a complex radical, have the suffix *o* attached to their names, which are then placed before the name of the metal. The acid radical is placed first in this case, then the names of the groups which replace the NH_3 radicals in the compound, and finally, immediately before the name of the metal, comes the number of ammonia molecules in the compound. These ammonia molecules, having different properties from the ordinary ammonia molecule, are distinguished by being called Ammino. Similarly, molecules of water in the salt are designated Aquo. All atoms or atom groups which are not directly united to the complex radical containing the metallic atom have their names placed after the name of the metal.

§ III. *THE STRUCTURE OF THE MOLECULAR COMPOUNDS OF COBALT.*

Some metals have the property of uniting with several molecules of ammonia to form complex radicals which are able to act as single ions. The greatest number of ammonia groups which can be united to a single metallic atom appears to be six. In the case of the cobalt compounds, since the metal can act both as a dyad and a triad, two classes of ammonia derivatives are known, one of which corresponds to the divalent state, while the other series is derived from the trivalent atom. For the present purpose the latter compounds are of more importance than the former.

There are four compounds formed by the union of ammonia with the compound CoX_3, in which X represents an acid radical: and we may write down the formulæ of these substances in the following way:—

$$CoX_3 + 3NH_3;\ CoX_3 + 4NH_3;\ CoX_3 + 5NH_3;\ CoX_3 + 6NH_3$$

These formulæ, however, do not represent the most salient differences between the compounds, which differences appear when they undergo ionisation. It is found that in some

members of the series the acid radicals X appear to lose their acid properties, for they can no longer be ionised away from the main complex of the molecule. In order to express this behaviour it will be necessary to devise new formulæ. This can best be done by placing the inactive radicals X within a large bracket along with the rest of the molecule, and leaving outside those acid radicals which still possess the property of undergoing ionisation. When this is done, the results are as follows :—

$$\begin{bmatrix} X_3 \\ Co \\ (NH_3)_3 \end{bmatrix} \quad \begin{bmatrix} X_2 \\ Co \\ (NH_3)_4 \end{bmatrix} X \quad \begin{bmatrix} X \\ Co \\ (NH_3)_5 \end{bmatrix} X_2 \quad \begin{bmatrix} Co \\ (NH_3)_6 \end{bmatrix} X_3$$

Now there is a compound trinitritotriamminocobalt which appears to have the properties represented by the formula :—

$$\begin{bmatrix} (NO_2)_3 \\ Co \\ (NH_3)_3 \end{bmatrix}$$

for although it contains three nitro-groups it has no true acid radical; that is to say, it gives rise to no ions when in aqueous solution. This behaviour can be accounted for only if we suppose that all the acid groups are directly attached to the cobalt atom, as is shown in the formula :—

$$(NH_3)_3Co \begin{cases} NO_2 \\ NO_2 \\ NO_2 \end{cases}$$

for if they were united to the ammonia radicals they would act as they do in ammonium nitrite, and dissociation would be possible.

The question of the ammonia groups must now be dealt with. It has been found that one of these can be replaced by a nitrito-radical, and that in the compound resulting from such a substitution all four nitrito-radicals have exactly the same properties as the three had in the trinitrito-compound. The formula for the tetranitrito-substance can be written thus :—

$$\left[Co\begin{matrix}(NO_2)_4\\(NH_3)_2\end{matrix}\right]R$$

This shows that one of the three ammonia groups is directly attached to the cobalt atom; and it is almost certain that the other two are similarly joined, as without such an assumption it is difficult to explain the fact that their chemical behaviour shows them to be completely separated from the acid radicals. The formulæ for the tetranitrito-diamminocobalt above might therefore be written as :—

$$\begin{matrix}NH_3 & & \\ & Co & \begin{matrix}NO_2\\NO_2\\NO_2\\NO_2\end{matrix}\\ NH_3 & & \end{matrix}$$

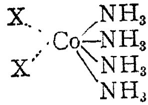
The action of ammonia upon the triammino-salts produces a series of compounds in which ammonia replaces the acid radicals in succession, causing them to alter their character, and become ionisable, thus :—

$$\left[(NH_3)_3Co\begin{matrix}NO_2\\NO_2\\NO_2\end{matrix}\right] + NH_3 = \left[(NH_3)_3Co\begin{matrix}NO_2\\NO_2\\NH_3\end{matrix}\right]NO_2$$

$$\left[(NH_3)_3Co\begin{matrix}NO_2\\NO_2\\NH_3\end{matrix}\right]NO_2 + NH_3 = \left[(NH_3)_3Co\begin{matrix}NO_2\\NH_3\\NH_3\end{matrix}\right]\begin{matrix}NO_2\\NO_2\end{matrix}$$

$$\left[(NH_3)_3Co\begin{matrix}NO_2\\NH_3\\NH_3\end{matrix}\right]\begin{matrix}NO_2\\NO_2\end{matrix} + NH_3 = \left[(NH_3)_3Co\begin{matrix}NH_3\\NH_3\\NH_3\end{matrix}\right]\begin{matrix}NO_2\\NO_2\\NO_2\end{matrix}$$

From the stereo-chemical point of view, however, we need deal only with the diacido-tetramminocobalt ammonias, whose formula is—



§ IV. *THE SPACE FORMULÆ OF THE MOLECULAR COMPOUNDS.*

The structural formula for the hexamminic cobalt salts is :—

$$\begin{bmatrix} NH_3 & & NH_3 \\ NH_3 & Co & NH_3 \\ NH_3 & & NH_3 \end{bmatrix} X_3$$

If we attempt to find a space formula corresponding to such a structural one, it is obvious that we must arrange all six ammonia radicals symmetrically around the cobalt atom ; for if they were not thus symmetrically arranged their properties would probably differ in each case. Now six points can be thus symmetrically arranged in space if they are placed at the corners of a regular octohedron :—

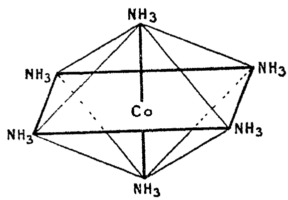
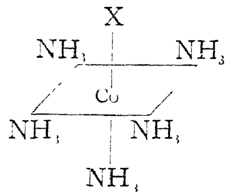


FIG. 44.

Since it would be almost impossible to discover the true space position of the X radicals, owing to the ease with which these are separated from the rest of the molecule by dissociation, it will not be necessary to define their relations to the rest of the complex.

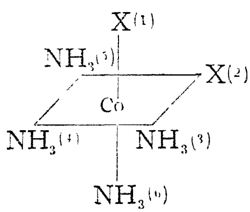
When we apply the above space formula to the case of the compounds containing five molecules of ammonia, we shall obtain the following symbol, in which the non-ionisable X radical is shown directly attached to the central cobalt atom :—

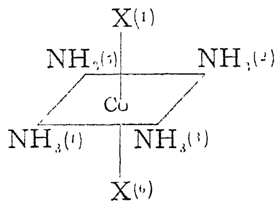


The first case where isomerism becomes possible is that of the diacido-tetramminic salts of the type :—

$$\left[\mathrm{Co}\begin{matrix}\mathrm{X_2} \\ \mathrm{(NH_3)_4}\end{matrix}\right]\mathrm{X}$$

Here a second acidic radical must enter into direct union with the cobalt atom, and it is apparent that this may occur in two ways: the two radicals may be at the ends of the same edge, as in the first figure; or at the opposite ends of a diagonal, as in the second figure :—





Compounds of this type may thus occur in two isomeric forms which will differ from one another but little in their chemical properties, since these are for the most part due to the ionisable radicals which play no part in the isomerism.

A series of such isomers will now be described, some of which contain ammonia radicals, while in others ammonia is replaced by amino-compounds. The compounds derived from ethylene diamine, which correspond to the formula $(X_2Co.en_2)X$ have been most closely studied. Here en_2 represents two molecules of ethylene-diamine, $NH_2CH_2CH_2NH_2$, and is equivalent to four molecules of ammonia.

§ V. TYPES OF THE STEREOISOMERIC COMPOUNDS

1. Dinitritotetrammino cobalt salts : $\left[Co \begin{matrix} (NO_2)_2 \\ (NH_3)_4 \end{matrix} \right] X$

    Flavo-salts discovered by Jorgensen.[1]
    Croceo-salts discovered by Gibbs.[2]

2. Disulphitotetrammino cobalt salts : $\left[Co \begin{matrix} (SO_3)_2 \\ (NH_3)_4 \end{matrix} \right] R$

    Reference may be made to the work of Hofmann and Reinsch,[3] Werner and Grüger,[4] and Hofmann and Jenny.[5]

3. Dichlorodiethylenediammino cobalt salts : $(Cl_2Co.en_2)X$

    Violeo-salts } discovered by Jorgensen.[6]
    Praseo-salts }

4. Dibromodiethylenediammino cobalt salts : $(Br_2.Co.en_2)X$

    Violeo-salts discovered by Werner.[7]
    Praseo-salts discovered by Jörgensen.[8]

5. Chloronitritodiethylenediammino cobalt salts :

    $(Cl.NO_2.Co.en_2)$

    Discovered by Werner and Gerb.[9]

6. Dinitritodiethylenediammino cobalt salts:

    $[(NO_2)_2Co.en_2]X$

    Discovered by Werner and Humphrey.[10]

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[1] Jorgensen, *Zeit. anorgan. Chem.*, **5**, 147 (1894) ; **19**, 145 (1899)
[2] Gibbs, *Proc. Amer. Acad. Arts and Science*, **10**.
[3] Hofmann and Reinsch, *Zeit. anorgan. Chem.*, **16**, 389 (1898).
[4] Werner and Gruger, *ibid.*, **16**, 398 (1898).
[5] Hofmann and Jenny, *Ber.*, **34**, 3857 (1901).
[6] Jörgensen, *J. pr. Chem.*, [2], **41**, 448 (1890).
[7] Werner, *Lehrbuch der Stereochemie*, p. 326.
[8] Jorgensen, *J. pr. Chem.*, [2], **41**, 440 (1890).
[9] Werner and Gerb, *Ber.*, **34**, 1739 (1901).
[10] Werner and Humphrey, *ibid.*, **34**, 1719 (1901).

7. Dithiocyanatodiethylenediammino cobalt salts :—

$$\left[Co \begin{matrix} (SCN)_2 \\ \\ en_2 \end{matrix} \right] X$$

Discovered by Werner and Braunlich.[1]

§ VI. *THE PREPARATION OF THE STEREOISOMERIC COBALT COMPOUNDS.*

1. Dinitritotetrammino salts of the type : $\left[Co \begin{matrix} (NO_2)_2 \\ (NH_3)_4 \end{matrix} \right] X$

The one series of isomers, croceo-salts, is produced by allowing the air to oxidise ammonical solutions of cobalt salts, to which nitrites have been added. Salts of this series may also be obtained by the action of nitrous acid upon nitrito-pentamminic salts :—

$$\left[Co \begin{matrix} (NO_2) \\ (NH_3)_5 \end{matrix} \right] (NO_2)_2 + HNO_2 = N_2 + 2H_2O + \left[Co \begin{matrix} (NO_2)_2 \\ (NH_3)_4 \end{matrix} \right] NO_2$$

The other isomers, flavo-salts, are formed by the action of nitrites or nitrous acid on chloroaquo- or diaquo-tetrammino salts :—

$$\left[Co \begin{matrix} Cl \\ OH_2 \\ (NH_3)_4 \end{matrix} \right] X_2 + 3NaNO_2 = 2NaX + NaCl + \overset{+H_2O}{} \left[Co \begin{matrix} (NO_2)_2 \\ (NH_3)_4 \end{matrix} \right] NO_2$$

$$\left[Co \begin{matrix} OH_2 \\ OH_2 \\ (NH_3)_4 \end{matrix} \right] X_3 + 3NaNO_2 = 3NaX + 2H_2O + \left[Co \begin{matrix} (NO_2)_2 \\ (NH_3)_4 \end{matrix} \right] NO_2$$

A mixture of the two isomers is produced when sodium nitrite acts upon the green (praseo) dichlorotetrammino salt :—

$$\left[Co \begin{matrix} Cl_2 \\ (NH_3)_4 \end{matrix} \right] Cl + 3NaNO_2 = 3NaCl + \left[Co \begin{matrix} (NO_2)_2 \\ (NH_3)_4 \end{matrix} \right] NO_2$$

---

[1] Werner and Braunlich, *Zeit anorgan. Chem.*, **22**, 91 (1900.)

2. Disulphitotetrammino salts of the type: $\left[Co\begin{matrix}(SO_3)_2\\ \\(NH_3)_4\end{matrix}\right]R$

The ammonium and sodium salts of the one series are formed by allowing sodium sulphite to act upon an oxidised ammoniacal solution of cobalt chloride. The two isomeric ammonium salts are formed simultaneously by oxidising an ammoniacal solution of cobalt acetate, saturating it with sulphurous acid, and filtering off the precipitate. They can be separated from one another by fractionally crystallizing the filtrate.

3. Dichlorodiethylenediammino salts of the type: $\left[Co\begin{matrix}Cl_2\\ \\en_2\end{matrix}\right]X$

The praseo salts are produced by the following method. The calculated quantity of ethylene diamine is added to a solution of cobalt chloride; air is then drawn through the solution to oxidise it. Afterwards, excess of hydrochloric acid is added, and the solution is evaporated. The violeo-salts are obtained by the evaporation of a solution of the *neutral* chloride of the praseo-salt.

4. Dibromodiethylenediammino salts of the type: $\left[Co\begin{matrix}Br_2\\ \\en_2\end{matrix}\right]X$

These are obtained by reactions similar to those used in the case of the dichloro-compounds.

5. Chloronitritodiethylenediammino salts of the type:

$$\left[CoNO_2\begin{matrix}Cl\\ \\en_2\end{matrix}\right]X$$

The 1,2-salts (corresponding to the flavo-series) are formed when neutral solutions of the green dichlorodiethylenediammino salts are treated with sodium nitrite; and also when green dichlorodiethylenediammino cobalt nitrite is moistened with water:—

$$\left[\mathrm{Co}\begin{matrix}\mathrm{Cl_2}\\ \\ \mathrm{en_2}\end{matrix}\right]\mathrm{Cl} + 2\mathrm{NaNO_2} = 2\mathrm{NaCl} + \left[\mathrm{Co}\begin{matrix}\mathrm{Cl}\\ \mathrm{NO_2}\\ \mathrm{en_2}\end{matrix}\right]\mathrm{NO_2}$$

Green dichloro-diethylenediammine   1,2-Chloronitrito-nitrite.

$$\left[\mathrm{Co}\begin{matrix}\mathrm{Cl_2}\\ \\ \mathrm{en_2}\end{matrix}\right]\mathrm{NO_2} \xrightarrow{\mathrm{H_2O}} \left[\mathrm{Co}\begin{matrix}\mathrm{Cl}\\ \mathrm{NO_2}\\ \mathrm{en_2}\end{matrix}\right]\mathrm{Cl}$$

Green dichloronitrite.   1,2-Chloronitritochloride.

The 1,6-salts (corresponding to the croceo-series) are obtained from the 1,6-nitrate by double decomposition. The nitrate itself is prepared by evaporating an aqueous solution of the 1,2-chloronitritonitrate; or by the action of hydrochloric acid upon croceo-diethylenediammino salts :—

$$\left[\mathrm{Co}\begin{matrix}\mathrm{(NO_2)_2}\\ \\ \mathrm{en_2}\end{matrix}\right]\mathrm{NO_3} + \mathrm{HCl} = \mathrm{HNO_2} + \left[\mathrm{Co}\begin{matrix}\mathrm{Cl}\\ \mathrm{NO_2}\\ \mathrm{en_2}\end{matrix}\right]\mathrm{NO_3}$$

6. **Dinitritodiethylenediammino salts of the type:**

$$\left[\mathrm{Co}\begin{matrix}\mathrm{(NO_2)_2}\\ \\ \mathrm{en_2}\end{matrix}\right]\mathrm{X}$$

A mixture of the two isomeric nitrites is produced when ethylenediamine acts on potassium-hexanitrito-cobalt :—

$$[\mathrm{Co}\,(\mathrm{NO_2})_6]\mathrm{K_3} + 2\mathrm{C_2H_4(NH_2)_2} = 3\mathrm{KNO_2} + \left[\mathrm{Co}\begin{matrix}\mathrm{(NO_2)_2}\\ \\ \mathrm{en_2}\end{matrix}\right]\mathrm{NO_2}$$

When silver nitrite is allowed to act upon 1,2-dichloro-diethylenediammino cobalt chloride (violeo-salt) an almost quantitative yield of the flavo-dinitritodiethylenediammino salt is formed: when the 1,6-isomer is used instead of the 1,2-compound, a sixty per cent. yield of the croceo-isomer is obtained.

The action of silver nitrite or sodium nitrite upon 1,2-chloronitrito salts produces a flavo-salt; while croceo-salts are produced by the same reaction from 1,6-chloronitrito salts.

7. Dithiocyanatodiethylenediammino salts of the type:

$$\left[Co \begin{matrix} (SCN)_2 \\ \\ en_2 \end{matrix} \right] X$$

A mixture of the two isomers is produced by the action of potassium thiocyanate upon 1,6-dichlorodiethylenediammino cobalt chloride. By varying the conditions of the reaction, one of the two isomers can be produced in greater quantity than the other.

§ VII. *THE PROPERTIES OF THE STEREOISOMERIC COBALTAMINE SALTS.*

1. Physical Properties.—The isomers differ from each other in many physical properties. The following table shows the colours of certain series; it will be seen that the differences are well marked:—

	Flavo-, 1,2- or violeo-salts.	Croceo-, 1,6- or praseo-salts.
$\left[Co \begin{matrix} (NO_2)_2 \\ \\ (NH_3)_4 \end{matrix} \right] NO_2$	Dark yellow-brown	Light yellow-brown
$\left[Co \begin{matrix} (SO_3)_2 \\ \\ (NH_3)_4 \end{matrix} \right] R$	Brown	Reddish yellow
$\left[Co \begin{matrix} Cl_2 \\ \\ en_2 \end{matrix} \right] X$	Violet	Green
$\left[Co \begin{matrix} Cl \\ NO_2 \\ en_2 \end{matrix} \right] X$	Scarlet	Orange
$\left[Co \begin{matrix} (NO_2)_2 \\ \\ en_2 \end{matrix} \right] X$	Brown	Yellow

In crystalline form and solubility the isomers differ from one another.

2. Chemical Properties.—In most reactions the groups concerned are the two ions into which the substance dissociates in solution; and since in the case of the cobaltamine salts the ions have the same properties in both isomers, there is little reason to expect great differences between them in so far as ordinary chemical properties are concerned. It is only when we come to deal with reactions in which the groups within the complex radical are concerned that we can reasonably expect to find any differences between the two isomers. Some examples of such reactions may now be given.

The action of concentrated hydrochloric acid upon the two varieties of the dinitritotetrammino cobalt salts is different in the case of each isomer; the croceo-salt gives rise to a chloronitrito-derivative, while the flavo-salt yields a chloroaquotetramminic compound:—

$$\underset{\text{Croceo-salt.}}{\left[Co\begin{matrix}(NO_2)_2\\ \\ (NH_3)_4\end{matrix}\right]Cl} + HCl = HNO_2 + \underset{\text{Chloronitritotetramminic salt.}}{\left[Co\begin{matrix}Cl\\ NO_2\\ (NH_3)_4\end{matrix}\right]Cl}$$

$$\underset{\text{Flavo-salt.}}{\left[Co\begin{matrix}(NO_2)_2\\ \\ (NH_3)_4\end{matrix}\right]Cl} + 2HCl + H_2O = 2HNO_2 + \underset{\text{Chloroaquotetramminic salt.}}{\left[Co\begin{matrix}Cl\\ OH_2\\ (NH_3)_4\end{matrix}\right]Cl_2}$$

Sodium nitrite has a different effect upon the two series of chloronitritodiethylenediammino salts; in the case of the 1,2-salts, flavo-salts are thus formed, while the 1,6-salts give croceo-compounds:—

$$\left[Co\begin{matrix}Cl\\ NO_2\\ en_2\end{matrix}\right]X + 2NaNO_2 = NaX + NaCl + \left[Co\begin{matrix}(NO_2)_2\\ \\ en_2\end{matrix}\right]NO_2$$

It seems probable that the two isomeric series of dithiocyanatodiethylenediammino salts may be not only different in configuration, but also structurally isomeric: in the one case the thiocyanate group being attached to the cobalt by means of the nitrogen atom, while in the other case the sulphur atom

forms the link between the two. This is rendered probable by the difference between the compounds which is shown on oxidation. In one case the nitrogen is left in ammonia attached to the cobalt atom; while in the other case it is eradicated completely. The structural differences would be expressed by the following formulæ :—

$$\left[\begin{matrix} & NCS\ (1) \\ Co & NCS\ (2) \\ & en_2 \end{matrix}\right]X \qquad \left[\begin{matrix} & SCN\ (1) \\ Co & SCN\ (6) \\ & en_2 \end{matrix}\right]X$$

These salts show differences also in the effect of acids upon them: the 1,6-salt being much more easily attacked than the 1,2-compound.

§ VIII. *THE TRANSMUTATION OF THE STEREO-ISOMERIC COBALT COMPOUNDS.*

Both direct and indirect transmutation has been observed in the case of these stereoisomers. Our information, however, is very scanty at present, and it will only be necessary to give one or two illustrations of the phenomena without entering into great detail.

It has been observed that the praseo-salts of the dichloro-diethylenediamines are stable in acid solution, but unstable in neutral solution; while the converse is true for the violeo-salts.* In order to convert the praseo-salt into its stereoisomer, all that is necessary is to prepare a neutral solution of the former and allow it to evaporate, when violeo-salt crystals are formed. Similarly, the violeo-salt can be changed into the corresponding praseo-salt merely by acidifying its solution with a mineral acid. In a somewhat similar manner, by evaporating their solutions the 1,6-salts of the dinitritodiethylenediamine series are changed into the 1,2-variety.

Indirect transmutation through an intermediate compound has been observed in the case of dinitritotetrammino salts.

* This recalls the analogous case of the oximes in acid and alkaline solution which was mentioned on p. 237.

The flavo-salt, by the successive actions of nitric acid and sodium nitrite, yields the croceo-isomer: a nitritonitratotetrammino salt being the intermediate substance:—

$$\left[Co\begin{matrix}(NO_2)_2\\ \\(NH_3)_4\end{matrix}\right]NO_3 + HNO_3 = HNO_2 + \left[Co\begin{matrix}NO_2\\NO_3\\(NH_3)_4\end{matrix}\right]NO_3$$

Flavo-salt. Nitritonitratotetrammino salt.

$$\left[Co\begin{matrix}NO_2\\NO_3\\(NH_3)_4\end{matrix}\right]NO_3 + 2NaNO_2 = 2NaNO_3 + \left[Co\begin{matrix}(NO_2)_2\\ \\(NH_3)_4\end{matrix}\right]NO_2$$

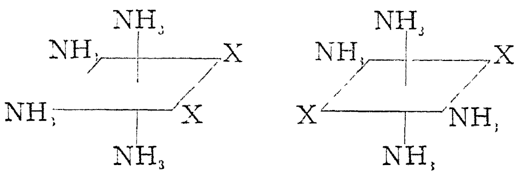
Nitritonitrato-salt. Croceo-salt.

§ IX. *THE DETERMINATION OF THE CONFIGURATION OF STEREOISOMERIC COBALT COMPOUNDS.*

1. **General.**—If the two isomeric forms of the radical:—

$$\left[Co\begin{matrix}X_2\\ \\(NH_3)_4\end{matrix}\right]$$

be written down, it becomes evident that they resemble to some extent the two isomeric acids, maleic and fumaric.

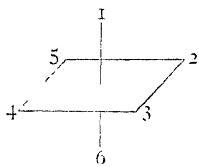


$$\begin{matrix}H—C—COOH\\ \|\\ H—C—COOH\end{matrix} \qquad \begin{matrix}H—C—COOH\\ \|\\ COOH—C—H\end{matrix}$$

From analogy, we call the case where the two X radicals lie on the same edge of the octahedron the cis-position; while the other case, in which they lie diagonally opposite to one another, may be termed the trans-position. The problem of configuration determination is to discover which of the positions

the X radicals occupy in any given compound. Now, it is not at present possible to determine with certainty the actual space positions of the radicals; but we can proceed somewhat in the same way as in the case of the sugar configurations, by showing that certain compounds are closely related to one another, and therefore probably have the same type of configuration. This *relative configuration determination* will now be dealt with.

2. Relative Configuration Determination.—Werner chooses as his starting-point the dichlorodiethylenediammino cobalt salts, and arbitrarily ascribes to the violet ones the name 1,2-salts, and to the green ones the name 1,6-salts. The figures are supposed to represent the positions shown on the figure below:—



The 1,2-compounds are thus cis- and the 1,6-series trans-derivatives.

Now, the 1,6-dichloro salts, derived either from ammonia or from ethylene diamine, are genetically related to the croceo-dinitrito salts, so Werner deduces that the croceo-salts are also 1,6-compounds, while the flavo-salts of the same series are 1,2-derivatives.

Red chloronitritodiethylenediammino salts yield flavo salts when treated with sodium nitrite; they are therefore 1,2-compounds, while the orange-coloured isomers which produce croceo-salts when similarly treated are 1,6-derivatives.

When potassium thiocyanate is allowed to act upon 1,2-dichlorodiethylenediammino cobalt salts the products are a series of soluble dithiocyanatodiethylenediammino cobalt salts. On the other hand, when the 1,6-salts are so treated, a more insoluble compound is produced, the yield of which can be increased by using more concentrated solutions. Now, in the concentrated solution the change from the 1,6- to the 1,2-variety is less than in dilute solutions, so that we may deduce

that the less soluble compound is formed directly from the 1,6-type; while the easily soluble substance belongs to the 1,2-group.

From a comparison of the properties of the isomeric disulphitotetrammino cobalt, ammonium, and sodium salts it has been deduced that the brown salts belong to the 1,2-series, while the reddish-yellow ones are 1,6-compounds.

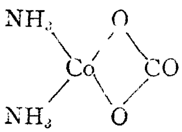
3. Absolute Configuration Determination. — Werner's reasons for the assumption that violeo-salts are 1,2-compounds and praseo-salts 1,6-ones are as follows:—

1. In other cases of geometrical isomerism it has been shown that the cis-compound is less stable than the trans-derivative. By analogy, the violeo-salts, being the less stable variety, should belong to the cis-series.

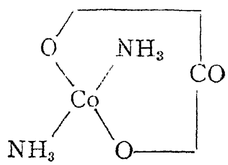
2. Intramolecular ring-formation is most easily produced when the reacting groups are in the cis-position to one another. It seems probable that in the carbonatotetrammino salts,

$$\left[\mathrm{Co}\begin{matrix}\mathrm{CO_3}\\ (\mathrm{NH_3})_4\end{matrix}\right]\mathrm{X},$$

the two oxygen atoms are attached to the cobalt atom in the cis-position, (I.), and not in the trans-position, (II.):—



(I.)



(II.)

Now, if the carbonato-salts belong to the cis-series the violeo-salts must also be of this type, since the carbonato-salts are converted into the violeo-salts by nitrous acid.

3. In the praseo-series the two acid radicals can act quite independently of one another, but in the violeo-salts this is not always the case. It therefore seems probable that in the violeo-salts the acid radicals lie nearer to one another than is the case in the praseo-salts. The violeo-salts would thus be cis-compounds.

CHAPTER VI.

STEREOISOMERISM IN PLATINUM COMPOUNDS.

IN the previous chapter it was stated that only one class of the cobaltamine derivatives, the tetrammino-compounds, showed any signs of being able to exist in stereoisomeric forms. In the platinum compounds, however, there are two series, both of which contain certain stereoisomeric types: the two classes are (A) derivatives of divalent platinum, and (B) derivatives of quadrivalent platinum. These will now be dealt with in turn.

A.—ISOMERIC DERIVATIVES OF DIVALENT PLATINUM.

§ I. *PROOF OF THE STRUCTURAL FORMULA.*

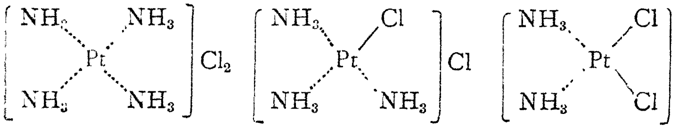
There are three chief classes of the ammonium addition products of divalent platinum salts, which may be expressed by the following general formulæ :—

$$\left[Pt\,(NH_3)_4\right]X_2 \qquad \left[Pt\begin{matrix} X \\ (NH_3)_3\end{matrix}\right]X \qquad \left[Pt\begin{matrix} X_2 \\ (NH_3)_2\end{matrix}\right]$$

If a chlorine atom be substituted for X in the above formulæ, we have a series of compounds, all of which are known :—

$$\underset{\text{(I.)}}{\left[Pt\,(NH_3)_4\right]Cl_2} \qquad \underset{\text{(II.)}}{\left[Pt\begin{matrix} Cl \\ (NH_3)_3\end{matrix}\right]Cl} \qquad \underset{\text{(III.)}}{\left[Pt\begin{matrix} Cl_2 \\ (NH_3)_2\end{matrix}\right]}$$

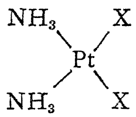
Now, it is found that in aqueous solution the compound (III.) does not ionise; the compound (II.) under the same circumstances gives rise to two ions; while the compound (I.) produces three ions. This is implied in the above formulæ, for if we regard the atoms within the square bracket as being firmly attached to one another, while those outside are easily ionised, the required number of ions would be produced in each case. The same may be expressed in a slightly different way by the formulæ below:—



It is evident that in such a series as the above we are dealing with four atoms or radicals grouped around a fifth atom, and at first sight the case seems parallel to that of the asymmetric carbon atom. On closer examination, however, this resemblance disappears.

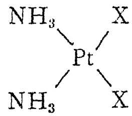
§ II. *THE SPACE FORMULAE OF THE DIVALENT PLATINUM STEREOISOMERS.*

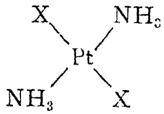
It has been found that compounds of the type:—



exist in two stereoisomeric forms. Since here we are dealing with two pairs of radicals, it is obvious that the asymmetry of the molecule cannot be the same as that shown by active carbon compounds, as the latter type requires the presence of four *different* radicals. If on this ground we exclude the tetrahedral arrangement of the four radicals, we are left with the only alternative hypothesis, *i.e.* that the four radicals lie in one

plane. If all four are distributed in this way, the two stereoisomeric compounds could be represented in this way :—



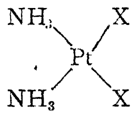


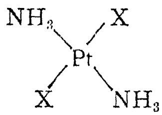
Up to the present, a considerable number of compounds have been synthesised which owe their isomerism to this cause, and it has been found that the radicle X may be very greatly varied. The most interesting case is that in which X is an amido-compound ; for here, although the four radicals have a similar chemical nature, the difference between the NH_3 and the amido-radicals suffices to produce the isomerism.

§ III. *THE NOMENCLATURE OF THE DIVALENT PLATINUM STEREOISOMERS.*

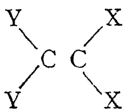
If the space formulæ of the platinum stereoisomers be compared with those of any pair of isomers in the ethylene series, the close resemblance between them will at once be noticed :—

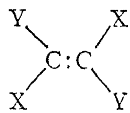
(I.)





(II.)





The first compound is therefore a *cis*-compound, while (II.) is a *trans*-compound. It is customary, however, to use a different nomenclature for this series of isomers ; those corresponding to the formula (I.) being called platosemidiammin

salts, while those corresponding to formula (II.) are termed platosammin salts.

§ IV. TYPES OF THE STEREOISOMERIC COMPOUNDS OF DIVALENT PLATINUM.

It is unnecessary to describe in detail all the stereoisomeric compounds of divalent platinum: it will be sufficient to give the method of preparation and the properties of the more important derivatives. The following list includes the compounds to be dealt with in the following sections:—

1. Platosemidiammin and platosammin salts—

Dichlorodiamminplatinum:[1] $Pt\begin{matrix}Cl_2\\(NH_3)_2\end{matrix}$

Disulphitodiamminplatinum.[2] $Pt\begin{matrix}(SO_3R)_2\\(NH_3)_2\end{matrix}$

Dichlorodipyridinplatinum.[3] $Pt\begin{matrix}(C_5H_5N)_2\\Cl_2\end{matrix}$

Triethyl phosphine compound:[4] $Pt\begin{matrix}[P(C_2H_5)_3]_2\\Cl_2\end{matrix}$

Ethyl sulphide compound:[5] $Pt\begin{matrix}[S(C_2H_5)_2]_2\\Cl_2\end{matrix}$

Ethyl selenide compound:[6] $Pt\begin{matrix}[Se(C_2H_5)_2]_2\\Cl_2\end{matrix}$

[1] Peyrone, *Annalen*, **51**, 1 (1844); **55**, 205 (1845), **61**, 178 (1847).
[2] Cleve, *Kon. Vet. Akad. Handl.*, **10**, No. 9, pp. 29, 52 (1872).
[3] Jorgensen, *J. pr. Chem.*, **33**, 504 (1886); Hedin, *Om pyridinens platinabaser s*, p. 8 (1887); *J. f. anorg. Chem.*, **3**, 314 (1893).
[4] Cahours, *Gal. Zeit.*, **1870**, 350, 437.
[5] Blomstrand, *J. pr. Chem.*, [2] **38**, 352, 358, 497 (1888); Klason, *Ber.*, **28**, 1493 (1895).
[6] Petrén, *Om Platinaäthylselenföreningar*, Lund (1898).

2. Tetramminplatinum compounds—

Dipyridindiamminplatochloride:[1] $\left[Pt \begin{matrix} (C_5H_5N)_2 \\ \cdot \\ (NH_3)_2 \end{matrix} \right] Cl_2$

Dipyridindiethylamminplatochloride:[2]

$$\left[Pt \begin{matrix} (C_5H_5N)_2 \\ (C_2H_5NH_2)_2 \end{matrix} \right] Cl_2$$

Dimethylammindiamminplatochloride:[3]

$$\left[Pt \begin{matrix} (NH_3)_2 \\ (CH_3NH_2) \end{matrix} \right] Cl_2$$

§ V. *THE PREPARATION OF THE STEREOISOMERIC DIVALENT PLATINUM COMPOUNDS.*

1. Dichlorodiamminplatinum: $Pt \begin{matrix} Cl_2 \\ (NH_3)_2 \end{matrix}$

The platosemidiamminchloride (cis-form) is prepared by the action of ammonia upon chloroplatinous salts:—

$$K_2PtCl_4 + 2NH_3 = Pt \begin{matrix} Cl_2 \\ (NH_3)_2 \end{matrix} + 2KCl$$

The platosamminchloride (trans-form) is obtained by heating tetramminplatochloride to 250° or by evaporating its solution in concentrated hydrochloric acid:—

$$Pt(NH_3)_4Cl_2 = Pt \begin{matrix} (NH_3)_2 \\ Cl_2 \end{matrix} + 2NH_3$$

[1] Jorgensen, *J. pr. Chem.*, **33**, 510 (1886).
[2] Jorgensen, *ibid.*, 530.
[3] Jörgensen, *ibid.*, **35**, 532 (1886).

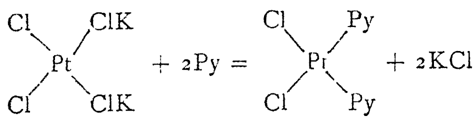
The other derivatives, bromo-, iodo-, nitrato-, or nitrito-compounds, are obtained from the chloride by double decomposition.

2. **Disulphitodiamminplatinum** : $Pt\begin{matrix}(SO_3H)_2\\(NH_3)_2\end{matrix}$

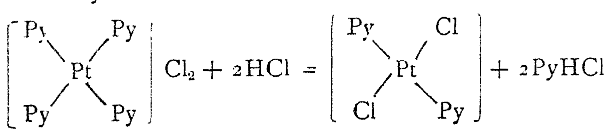
This is prepared from the chloride, the cis- or trans-compound being used as a starting-point according to which isomer is required.

3. **Dichlorodipyridinplatinum** : $Pt\begin{matrix}Py_2\\Cl_2\end{matrix}$

The cis-compound is prepared by the action of pyridine upon an aqueous solution of potassium chloroplatinite :—



The trans-compound is formed when $(PtPy_4)Cl_2$ is heated with excess of hydrochloric acid :—



4. **Triethylphosphineplatochloride** : $Pt\begin{matrix}[P(C_2H_5)_3]_2\\Cl_2\end{matrix}$

The cis-compound is obtained by boiling triethyl phosphine with platinum chloride solution; the trans-isomer is produced when the cis-chloride is heated to 100° with alcohol; also from tetraphosphinplatochloride by the loss of two molecules of phosphine.

5. **Ethyl selenide compound** : $Pt\begin{matrix}[Se(C_2H_5)_2]_2\\Cl_2\end{matrix}$

The α-chloride is formed by the action of ethyl selenide on

potassium chloroplatinite; the β-isomer is produced by boiling the α-compound with water and ethyl selenide.

6. **Dipyridindiamminchloride**: $\left[Pt \begin{matrix} Py_2 \\ (NH_3)_2 \end{matrix} \right] Cl_2$

The cis-compound is produced when cis-dichlorodiamminplatinum is dissolved in pyridine, or when cis-dichloropyridinplatinum is dissolved in ammonia. The trans-compound is obtained in the same way, trans-isomers being used instead of cis-compounds as starting-points.

7. **Dipyridindiethylamminplatochloride**: $\left[Pt \begin{matrix} Py_2 \\ (C_2H_5)_2 \end{matrix} \right] Cl_2$

The cis-compound is obtained by dissolving cis-dichlorodipyridinplatinum in an aqueous solution of ethylamine, or dissolving cis-dichlorodiethylaminplatinum in pyridine. The trans-compound is obtained similarly from the trans-isomers.

8. **Dimethylammindiamminplatochloride**: $\left[Pt \begin{matrix} (NH_3)_2 \\ (CH_3NH_2)_2 \end{matrix} \right] Cl_2$

The cis-compound is obtained by dissolving cis-dichlorodiamminplatinum in aqueous methylamine: the trans-compound is similarly prepared from the trans-isomer.

§ VI. *THE PROPERTIES OF THE STEREOISOMERIC DIVALENT PLATINUM COMPOUNDS.*

In general it may be said that the isomers differ in colour, in solubility, in melting-point, and also in crystalline form.

In chemical properties also the two series of isomers show very considerable differences. The following examples illustrate this.

The two isomeric disulphitodiamminplatinum compounds behave differently in salt formation; the trans-compound forms normal salts of the type:—

$$\mathrm{Pt}\begin{matrix}(\mathrm{NH_3})_2\\(\mathrm{SO_3R})_2\end{matrix}$$

while on the other hand the cis-isomer forms double salts of the following type :—

$$\mathrm{Pt}\begin{matrix}(\mathrm{NH_3})_2\\(\mathrm{SO_3Ag})_2\end{matrix}+\mathrm{Ag_2SO_3}\ ;\quad \mathrm{Pt}\begin{matrix}(\mathrm{NH_3})_2\\(\mathrm{SO_3NH_4})_2\end{matrix}+(\mathrm{NH_4})_2\mathrm{SO_3}$$

The action of ammonia upon the two isomeric forms of dichlorodipyridinplatinum is different ; it gives rise to two isomeric compounds having the formula :—

$$\left[\mathrm{Pt}\begin{matrix}(\mathrm{NH_3})_2\\\mathrm{Py_2}\end{matrix}\right]\mathrm{Cl_2}$$

Another difference between the two isomers lies in the fact that the cis-form gives anhydrous crystals, while the trans-form crystallizes with two molecules of water.

When the ethyl selenide compound :—

$$\mathrm{Pt}\begin{matrix}[\mathrm{Se}(\mathrm{C_2H_5})_2]_2\\\mathrm{Cl_2}\end{matrix}$$

is treated with silver nitrate, it is found that in the case of the cis-compound one chlorine atom reacts more readily than the other, which is not the case with the trans-isomer.

The action of hydrochloric acid upon the cis- and trans-isomer of dipyridindiamminchloride yields different results. In the case of the cis-compound, a compound of the formula :—

$$\mathrm{Pt}\begin{matrix}\mathrm{Cl_2}\\\mathrm{NH_3}\\\mathrm{Py}\end{matrix}$$

is produced, while with the trans-isomer a mixture of two substances is produced :—

$$\mathrm{Pt}\begin{matrix}\mathrm{Cl_2}\\(\mathrm{NH_3})_2\end{matrix}\qquad\qquad \mathrm{Pt}\begin{matrix}\mathrm{Cl_2}\\\mathrm{Py_2}\end{matrix}$$

§ VII. *CONFIGURATION DETERMINATION.*

The configuration of the platosammin and platosemidiammin salts has been determined by Werner in the following way. The complex :—

$$Pt \begin{matrix} Cl_2 \\ R_2 \end{matrix}$$

(where R is NH_3, pyridine, etc.) can combine with two more molecules of R to form the new complex $(PtR_4)Cl_2$, which can be broken down again by loss of R_2 into a complex of the original type. Now, if the second two molecules R be different in nature from the first two (*e.g.* if the original substance be :—

$$Pt \begin{matrix} Cl_2 \\ (NH_3)_2 \end{matrix}$$

and the new complex be formed by the addition of two molecules of pyridine), the two isomeric salts, platosammin and platosemidiammin, produce different compounds.

Now, if we take platosemidiamminchloride and treat it with pyridine, we shall produce a compound :—

$$\left[Pt \begin{matrix} (NH_3)_2 \\ Py_2 \end{matrix} \right] Cl_2,$$

which is identical with that produced by the action of ammonia upon platosemipyridinchloride. This compound we may term α for the sake of convenience :—

$$\left.\begin{matrix} Pt \begin{matrix} Cl_2 \\ (NH_3)_2 \end{matrix} + 2Py = \left[Pt \begin{matrix} (NH_3)_2 \\ Py_2 \end{matrix} \right] Cl_2 \\ \text{Platosemidiammin derivative.} \\ Pt \begin{matrix} Cl_2 \\ Py_2 \end{matrix} + 2NH_3 = \left[Pt \begin{matrix} (NH_3)_2 \\ Py_2 \end{matrix} \right] Cl_2 \end{matrix} \right\} \text{Identical, } \alpha\text{-compound.}$$

If, now, we treat the platosammin salts in the same way, we again obtain two identical compounds, but these two new compounds are not the same as the α-ones already produced. The new compound we may term β :—

$$\left.\begin{array}{c}\mathrm{Pt}\begin{matrix}(\mathrm{NH_3})_2\\ \mathrm{Cl_2}\end{matrix} + 2\mathrm{Py} = \left[\mathrm{Pt}\begin{matrix}(\mathrm{NH_3})_2\\ \mathrm{Py_2}\end{matrix}\right]\mathrm{Cl_2}\\ \text{Platosammin derivative}\\ \mathrm{Pt}\begin{matrix}\mathrm{Py_2}\\ \mathrm{Cl_2}\end{matrix} + 2\mathrm{NH_3} = \left[\mathrm{Pt}\begin{matrix}(\mathrm{NH_3})_2\\ \mathrm{Py_2}\end{matrix}\right]\mathrm{Cl_2}\end{array}\right\}\text{Identical, } \beta\text{-compound.}$$

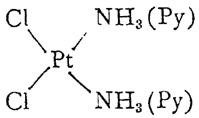
These two isomeric derivatives, α and β, differ from one another in various respects, but resemble each other in so far that when two of the basic radicals are split off, both compounds yield the same decomposition product, namely, a platosammin derivative. In order to do this, the α-compound splits off one molecule of ammonia and one molecule of pyridine; but in the case of β-compound the reaction is different, one molecule losing two ammonia radicals, while a second molecule loses two pyridine radicals :—

$$(\alpha)\quad \left[\mathrm{Pt}\begin{matrix}\mathrm{Py_2}\\ (\mathrm{NH_3})_2\end{matrix}\right]\mathrm{Cl_2} \longrightarrow \mathrm{Py} + \mathrm{NH_3} + \mathrm{Pt}\begin{matrix}\mathrm{Py}\\ \mathrm{NH_3}\\ \mathrm{Cl_2}\end{matrix}$$

$$(\beta)\quad \left[\mathrm{Pt}\begin{matrix}\mathrm{Py_2}\\ (\mathrm{NH_3})_2\end{matrix}\right]\mathrm{Cl_2} \begin{array}{l}\nearrow 2\mathrm{NH_3} + \mathrm{Pt}\begin{matrix}\mathrm{Py_2}\\ \mathrm{Cl_2}\end{matrix}\\[2ex] \searrow 2\mathrm{Py} + \mathrm{Pt}\begin{matrix}(\mathrm{NH_3})_2\\ \mathrm{Cl_2}\end{matrix}\end{array}$$

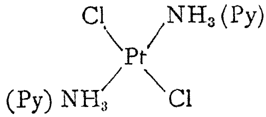
The courses of these two reactions can be explained only by assuming the following formulæ for the two series of compounds :—

Platosemidiammin compounds.



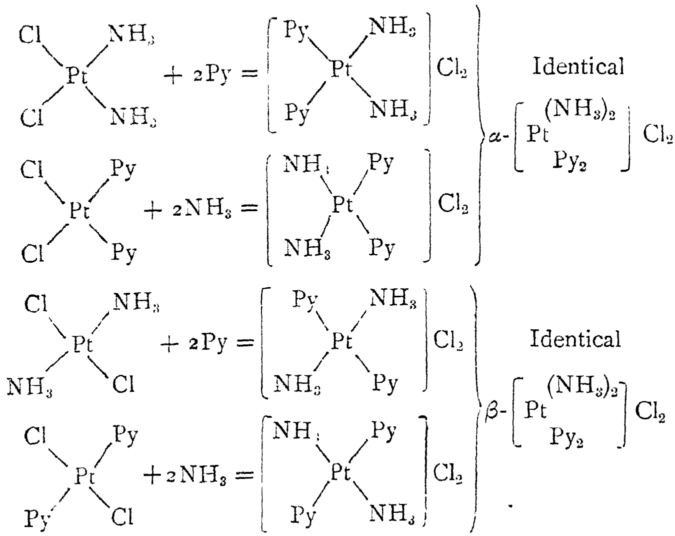
Cis-series.

Platosammin compounds.



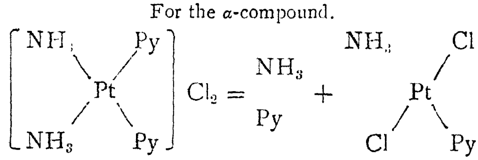
Trans-series.

On this assumption, the addition reactions will occur as follows :—

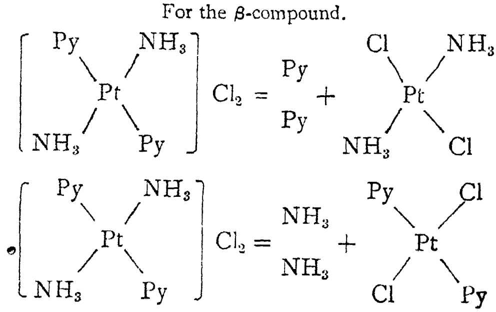


We must now consider the breakdown of these two isomers into the simple platosammin derivative. The reaction will be expressed by the following equations :—

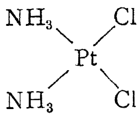
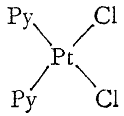
For the α-compound.



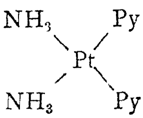
For the β-compound.



Objection may be made to this reasoning on the ground that the platosammin compounds might really be cis-derivatives instead of trans-compounds. This may be easily shown to be improbable. If we assume that the platosammin compounds have a cis-configuration :—

(I.)   (II.)

then the addition of ammonia to (II.) or of pyridine to (I.) would produce a cis-derivative :—



Now, such a compound could be changed into a platosammin derivative (assumed to be a cis-form) in three ways :—

1. By loss of two molecules of ammonia.
2. By loss of two molecules of pyridine.
3. By loss of one molecule of ammonia and one molecule of pyridine.

A mixture of the three compounds would thus be produced :—

$$(1)\ \mathrm{Pt}\begin{matrix}\mathrm{Py_2}\\ \mathrm{X_2}\end{matrix} \qquad (2)\ \mathrm{Pt}\begin{matrix}\mathrm{(NH_3)_2}\\ \mathrm{X_2}\end{matrix} \qquad (3)\ \mathrm{Pt}\begin{matrix}\mathrm{Py}\\ \mathrm{NH_3}\\ \mathrm{X_2}\end{matrix}$$

but such a case has not yet been observed.

§ VIII. *RESEMBLANCES BETWEEN ETHYLENE STEREOISOMERS AND THOSE OF DIVALENT PLATINUM.*

It has already been pointed out that the space formulæ for ethylene derivatives resemble those proposed for the

platinum isomers: this parallel can also be noted in the properties of the isomers of both series.

For instance, in the platinum isomers, as in the ethylene compounds, the cis-form is the less stable of the two, and can by various means be converted into the more stable trans-compound. It is also noteworthy that the cis-form is usually produced by less violent reactions than the trans-form. Just as in the ethylene series, the platinum cis-compounds appear to have lower melting-points than the corresponding trans-isomers; while the great solubility of the cis-forms also recalls the properties of the ethylene series. It has already been mentioned that in those cases where ethylene compounds are coloured, the cis-variety are more intensely tinted than the trans-forms; the same holds good in the platinum series.

B.—Isomeric Derivatives of Quadrivalent Platinum.

§ 1. *STRUCTURAL AND SPACE FORMULÆ.*

The metal-ammonia compounds of quadrivalent platinum resemble very closely those of cobalt, inasmuch as they may be supposed to be derived from a complex radical, $Pt(NH_3)_6$, just as the ammonia compounds of cobalt were derived from the complex $Co(NH_3)_6$. The compound containing the greatest number of ammonia is $[Pt(NH_3)_6]X_4$; and it is found that when any of these ammonia radicals is removed, its place is taken by one of the X radicals, which then forms part of the central radical, and ceases to be ionised when in solution. The case is perfectly parallel to that of the cobalt series. Thus, for instance, if two ammonia molecules are driven out of the nucleus, we get a compound of the form $[Pt(NH_3)_4]X_2$; and if four molecules of ammonia are expelled we obtain the compound:—

$$\left[Pt\begin{matrix}X_4\\(NH_3)_2\end{matrix}\right]$$

which does not ionise in solution.

The space formula for these platinum derivatives is assumed to be the same as that of the corresponding cobalt compounds; that is to say, the six groups are placed at the corners of an octahedron, at whose centre the cobalt atom lies.

§ II. *CASES OF ISOMERISM.*

As very little is as yet known of this series, it will be best to give a brief account of the properties and preparation of the best-known isomers :—

$$Pt\begin{matrix}Cl_4\\(NH_3)_2\end{matrix} \quad \text{and} \quad Pt\begin{matrix}Br_4\\(NH_3)_2\end{matrix}$$

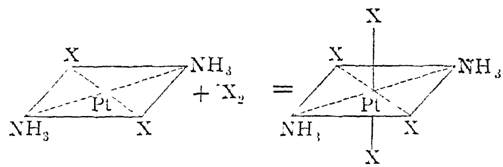
The form produced from a platosemidiammin compound has been termed a platinisemidiammin derivative, while the other isomer is termed a platiniammin compound.

Platinisemidiamminchloride is obtained by the action of chlorine upon cis-dichlorodiamminplatinum; the second isomer is produced by the addition of chlorine to trans-dichlorodiamminplatinum. The two isomers differ in colour, the one derived from the cis-form being orange-coloured, while the other is yellow. They differ also in conductivity and crystalline form.

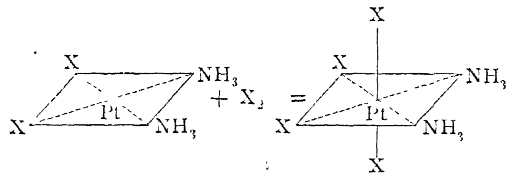
Platinisemidiamminbromide is formed from bromine and platosemidiamminbromide; its isomer is formed similarly from platosamminbromide. The two bromides differ in colour and crystalline form.

§ III. *CONFIGURATION DETERMINATION.*

The space formulæ of the two isomers can be deduced from the methods by which they are formed; the figures below illustrate the point :—



Platosammin salt. Platinammin salt.



Platosemidiammin salt. Platinsemidiammin salt.

CHAPTER VII.

STEREOISOMERISM IN CHROMIUM COMPOUNDS.

§ 1. *STRUCTURE OF THE STEREOISOMERIC COMPOUNDS OF CHROMIUM.*

P. Pfeiffer[1] has extended the ideas of Werner to the case of certain isomeric compounds of chromium. The bodies in question are simple addition products of ethylene-diamine and salts of trivalent chromium; they correspond to the empirical formula ($CrX_3 + 2en$), where en is used as a symbol for ethylene-diamine. Since in these compounds only one of the X radicals possesses ionic character, we may draw the same inferences in this case as were deduced by Werner in the case of the cobalt isomers. Adopting Werner's system, we should write the formulæ of these compounds in this way :—

$$\left[\mathrm{Cr}\begin{matrix}\mathrm{en}_2\\ \\ \mathrm{X}_2\end{matrix}\right]\mathrm{X}$$

which indicates that on ionisation the compound breaks up into two ions, one of which is X, the other being the radical contained within the square bracket. Thus the three X radicals are not equivalent, two being directly attached to the chromium atom, while the third is attached in some way to the whole of the group within the bracket.

Pfeiffer has found that salts of this type can exist in two isomeric forms ; the dithiocyanato-, dichloro-, and dibromo-

[1] Pfeiffer, *Ber.*, **37**, 4255 (1904) ; Pfeiffer and Trieschmann, *Annalen*, **342**, 283, 305 (1905).

isomers have been investigated. He heated triethylene-diamine-chromium thiocyanate, $[Cr\ en_3](SCN)_3$, and found that in this way one molecule of ethylene-diamine was liberated, and a salt of the formula :—

$$\left[Cr\begin{matrix}en_2\\ \\(SCN)_2\end{matrix}\right]SCN$$

remained behind. From this salt, by double decomposition, he obtained a whole series of salts of the type :—

$$\left[Cr\begin{matrix}en_2\\ \\(SCN)_2\end{matrix}\right]X$$

which he terms α-salts. Pfeiffer was also able to prepare the α-dithiocyanatothiocyanate by the action of ethylene-diamine upon potassium chromium thiocyanate. In this case, however, a second body is formed during the reaction; for together with the long, flat, orange-red needles of the α-salt appear small glittering orange-coloured scales of a β-salt. This β-salt may be obtained by another method, viz. the action of potassium thiocyanate upon bromo-aquo-diethylenediamine chromium bromide :—

$$\left[Cr\begin{matrix}en_2\\(OH_2)\\Br\end{matrix}\right]Br_2$$

When prepared in this manner, the β-salt is not contaminated by traces of the α-salt. Pfeiffer has been able to show that the two compounds are really isomers, and that we are not dealing with a case of mere isomorphism; this was proved by preparing a series of derivatives of the two sets of compounds, and showing that the derivatives in the α-series differed completely from those of the β-series, while salts of the α-series could always be converted into the original α-thiocyanate by treatment with potassium thiocyanate; while the same holds true for the β-salts, which yield the β-thiocyanate. The β-salts, therefore, appear to have the structure :—

$$\left[\begin{matrix}en_2\\Cr(SCN)_2\end{matrix}\right]X$$

in which the complex within the square bracket remains unaffected during any double decomposition which the salt may be made to undergo.

The evidence, however, does not exclude the possibility of structure isomerism, as the one series of salts (I.) might be akin to the true thiocyanates, while the other series (II.) resembled the isothiocyanates :—

$$\left[\begin{array}{l} \quad en_2 \\ Cr\,SCN \\ \quad SCN \end{array}\right]X \qquad\qquad \left[\begin{array}{l} \quad en_2 \\ Cr\,N{:}CS \\ \quad N{:}CS \end{array}\right]X$$

(I.) (II.)

But if this were the case, we should expect to find the two series of salts act in different ways when they were oxidised, as Werner and Bräunlich observed in the corresponding compounds of cobalt. From his results with oxidising agents, Pfeiffer was able to prove that there was no structure difference between the isomers. The isomerism must therefore be due to stereochemical causes.

The case for the stereochemical explanation gains force when it is noticed that the thiocyanate radicals, which are directly attached to the chromium atom, can be replaced by other groups, and that, in spite of this change, isomerism is still found in the derivatives, *e.g.* the addition product of two molecules of ethylene-diamine to chromium chloride exists in two isomeric forms :—

$$\left[Cr\begin{array}{l} en_2 \\ \\ Cl_2 \end{array}\right]X$$

This salt is obtained by treating the α-thiocyanatothiocyanate, suspended in water, with chlorine, whereby a green salt is produced. Its constitution is deduced in the following way. In its aqueous solution, neither chromium ions nor ethylene-diamine molecules can be detected; these together must therefore form a complex ion. Further, in the course of double decompositions, only one atom of chlorine enters into reaction; the other two, therefore, must be united to the chromium atom, and the salt has the constitution expressed in the formula.

Pfeiffer has prepared salts in which the group X is replaced by chlorine, bromine, iodine, the nitrate, thiocyanate, and dithionate radicals. All these salts were green in colour, and, for the sake of convenience, they may be referred to as "green dichloro-salts."

If we oxidise the β-thiocyanatothiocyanate we find that, instead of the green compound which was produced by the α-salt, a violet substance is formed, whose composition and constitution, determined by the means already mentioned, are identical with those of the green α-compound. From this new chloride it is possible to obtain a second series of salts of the general formula :—

$$\left[Cr \begin{matrix} en_2 \\ \\ Cl_2 \end{matrix} \right] X$$

which are all violet in colour. Without going into further detail, we may say that Pfeiffer has shown that, in general, the addition products of two molecules of ethylene-diamine to salts CrX_3 of trivalent chromium exist in two structurally identical isomeric forms. From their methods of preparation we can classify these substances as follows :—

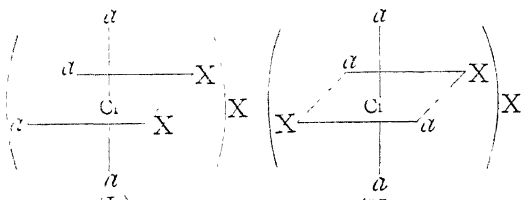
α-Dithiocyanato-salts.	β-Dithiocyanato-salts.
Green dichloro-salts	Violet dichloro-salts.

§ II. *THE SPACE FORMULÆ OF THE STEREOISOMERIC CHROMIUM COMPOUNDS.*

Since the chromium atom has the faculty of uniting with six other atoms, we are evidently dealing with a case analogous to that of cobalt; and the same arguments apply in this case as were used by Werner in the question of the space formulæ of the cobaltamines. Without repeating the reasoning, we may give the results arrived at in the present instance. Since compounds of the type $[Cr\ a_4X_2]X$ * exist in two isomeric

* It should be observed that this formula corresponds to $[Cr\ en_2X_2]$, as one molecule of ethylene-diamine replaces two molecules of ammonia.

forms, which must be due to a difference in the arrangement of their atoms in space, we may dispose these six groups a_4X_2 at the corners of an octahedron; and in this way we shall obtain two possible configurations, and only two :—



(I.) (II.)

Here, just as in the case of the cobalt compounds, we shall have two series of compounds, one of which, corresponding to the formula (I.), may be called the cis-form, while the other is the trans-form.

§ III. *THE PREPARATION OF THE STEREOISOMERIC CHROMIUM COMPOUNDS.*

It will be most convenient to describe separately the methods of preparation of the two series of isomers. We may deal first with the cis-compounds.

The compound from which most of the others can be derived, directly or indirectly, is bromo-aquo-diethylenediamine chromium bromide, which is prepared in the following manner. Hydrated chromium chloride is dissolved in pyridine; water is added, and the precipitate is dissolved in the least possible quantity of hydrochloric acid; the solution is filtered and precipitated with pyridine. The chloride thus obtained is evaporated on the water bath with a solution of ethylene diamine until it becomes syrupy. Concentrated fuming hydrobromic acid is then added drop by drop until no more gas is evolved. After standing a few days, the solution produces small compact red crystals of the required bromide :—

$$\left[Cr \begin{matrix} en_2 \\ (OH_2) \\ Br \end{matrix} \right] Br_2$$

From this substance we can obtain cis-dithiocyanato-diethylenediamine chromium thiocyanate :—

$$\left[Cr \begin{matrix} en_2 \\ \\ (SCN)_2 \end{matrix} \right] SCN$$

by double decomposition with potassium thiocyanate ; and from the thiocyanate in turn we can obtain the chloride :—

$$\left[Cr \begin{matrix} en_2 \\ \\ (SCN)_2 \end{matrix} \right] Cl$$

by warming it with hydrochloric acid.

The last compound of this series whose preparation need be described is the dithiocyanato-diethylenediamine chromium nitrate, which is formed when the solid thiocyanate salt is left in contact with concentrated nitric acid which has been diluted with thrice its bulk of water :—

$$\left[Cr \begin{matrix} en_2 \\ \\ (SCN)_2 \end{matrix} \right] NO_3$$

The cis-dichloro-diethylenediamine chromium salts of the general formula :—

$$\left[Cr \begin{matrix} en_2 \\ \\ Cl_2 \end{matrix} \right] X$$

are obtained, like the dithiocyanato salts, from a pyridine derivative. The method of preparation is the same as that used in the case of bromo-aquo-diethylenediamine chromium bromide, except that hydrochloric acid replaces hydrobromic acid. The salt thus obtained is the cis-dichloro-diethylene-diamine chromium chloride :—

$$\left[Cr \begin{matrix} en_2 \\ \\ Cl_2 \end{matrix} \right] Cl$$

From this chloride several other salts are obtained, *e.g.* the nitrate :—

$$\left[Cr\begin{matrix}en_2\\ \\Cl_2\end{matrix}\right]NO_3$$

by the action of concentrated nitric acid ; and the cis-dichloro-thiocyanate :—

$$\left[Cr\begin{matrix}en_2\\ \\Cl_2\end{matrix}\right]SCN$$

by double decomposition.

We must now turn to the salts of the trans-series. Trans-dithiocyanato chromium thiocyanate is obtained by heating triethylenediamine chromium thiocyanate, $[Cr\ en_3]\ (SCN)_3$, and from this in turn we can obtain dichloro-diethylenediamine chromium chloride by the successive actions of chlorine and hydrochloric acid. From the dichloro-chloride the dichloro-thiocyanate is produced by double decomposition with potassium thiocyanate. Just as the corresponding cis-compound was obtained by the action of concentrated nitric acid upon the cis-dichloro-chloride, so we obtain the trans-isomer of the type :—

$$\left[Cr\begin{matrix}en_2\\ \\Cl_2\end{matrix}\right]NO_3$$

by the action of concentrated nitric acid upon :—

$$\left[Cr\begin{matrix}en_2\\ \\Cl_2\end{matrix}\right]Cl$$

When a solution of cis-dichloro-diethylenediamine chromium chloride is warmed with a concentrated solution of potassium oxalate, the cooled solution deposits a crystalline carmine substance. The analysis of this substance proves it to have the empirical formula $Cr_2en_3(C_2O_4)_3$. From the manner of its production it appears probable that the salt has the constitution :—

$$\left[Cr\begin{matrix}en_2\\ \\C_2O_4\end{matrix}\right]\left[Cr\begin{matrix}en\\C_2O_4\\C_2O_4\end{matrix}\right]$$

This probability proves to be almost a certainty, as it has been found possible by the use of concentrated acids to expel the positive group :—

$$\left[Cr \begin{matrix} en_2 \\ \\ C_2O_4 \end{matrix} \right]$$

from the molecule, and to isolate it in the form of salts of the type :—

$$\left[Cr \begin{matrix} en_2 \\ \\ C_2O_4 \end{matrix} \right] X$$

On the other hand, when we treat trans-dichloro-diethylene-diamine in the same way, violet-red crystals separate from the cool solution. In contrast to the result in the case of the cis-compound, these crystals contain chlorine.

§ IV. *THE PROPERTIES OF THE STEREOISOMERIC CHROMIUM COMPOUNDS.*

Except in so far as the properties of the two isomers differ from one another, it will not be necessary to deal with them here. The chief difference between the two dithiocyanato-diethylenediamine chromium thiocyanates :—

$$\left[Cr \begin{matrix} en_2 \\ \\ (SCN)_2 \end{matrix} \right] SCN$$

is in colour and crystalline form ; the cis-compound being found in the form of small, reddish-orange scales which are made up of fine needles, while the trans-isomer occurs as long, gleaming, yellowish-red needles.

The chloride :—

$$\left[Cr \begin{matrix} en_2 \\ \\ (SCN_2) \end{matrix} \right] Cl$$

gives glittering, ruby-red needles in the cis-form, while the

trans-form consists of orange-red rhombic crystals. A further difference between the isomers appears to be their stability in aqueous solution, the cis-isomer decomposing faster than the trans-compound. The data, however, are not very exact on this point.

In the case of the nitrate :—

$$\left[Cr \begin{matrix} en_2 \\ (SCN)_2 \end{matrix} \right] NO_3$$

the cis-form crystallizes anhydrous, while the trans-form has one molecule of water of crystallization.

A similar difference is found in the case of the dichloro-diethylenediamine chromium chloride :—

$$\left[Cr \begin{matrix} en_2 \\ Cl_2 \end{matrix} \right] Cl$$

as the cis-form of this substance crystallizes with one molecule of water; while the trans-chloride is an acid salt, and crystallizes with two molecules of water and one of hydrochloric acid. On heating to 100° C., both lose their water of crystallization. The cis-compound does not change in colour with this loss, but the trans-chloride, which also loses its hydrochloric acid molecule, is converted into the green neutral chloride.

Finally, the dichloro-nitrate :—

$$\left[Cr \begin{matrix} en_2 \\ Cl_2 \end{matrix} \right] NO_3$$

shows differences in colour between the two isomeric forms. The cis-compound occurs as small, violet-red, needle-shaped leaflets. The trans-compound is made up of grey-green needles, which, when heated, become pure green in colour, but grow grey again on cooling. The trans-isomer is much less soluble in water than the cis-form.

§ V. *THE TRANSMUTATION OF THE STEREOISOMERIC COMPOUNDS OF CHROMIUM.*

In comparison with the isomeric cobalt compounds, the isomers of the chromium series are distinguished by a much greater degree of stability. For instance, it is possible to evaporate solutions of the green or violet salts in hydrochloric acid to dryness without bringing about any change in configuration, though in the case of the cobalt salts this method can be used as a means of transmuting one isomer into the other. In spite of this, however, it is possible to convert many chromium compounds of the one type into their stereoisomers.

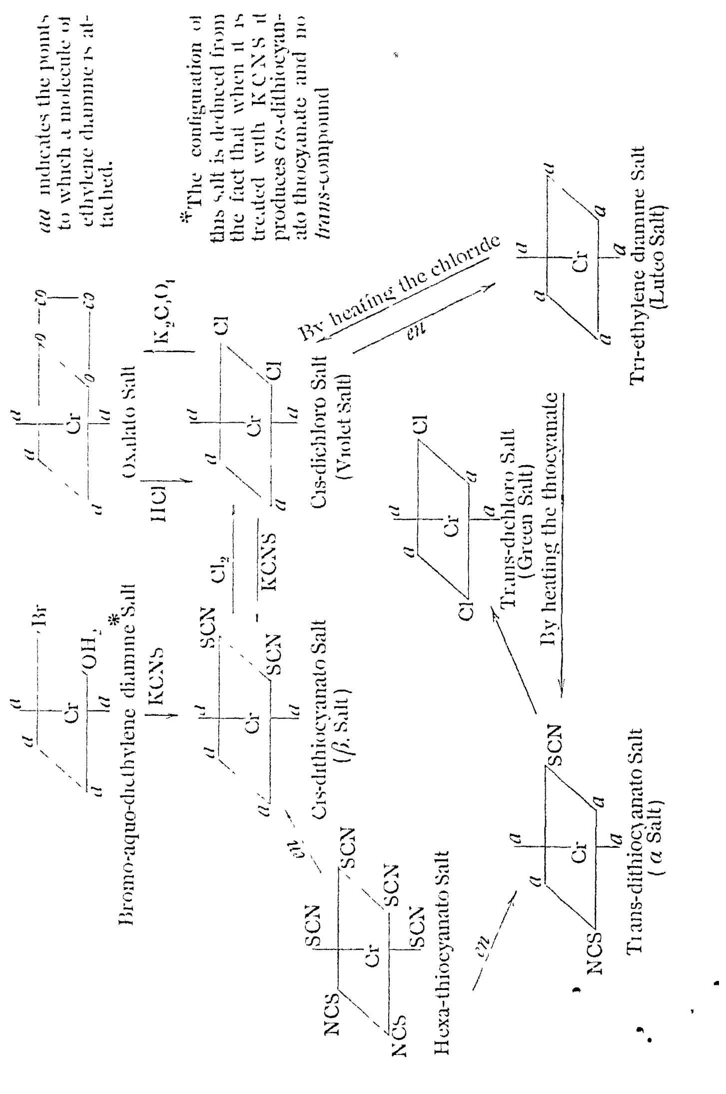
The change of a green salt into a violet one may be accomplished as follows. An aqueous solution of the green salt is allowed to stand for one or two days, during which time its colour changes to red; and on evaporating the solution with hydrochloric acid a considerable quantity of violet salt can be isolated.

The reverse change of a violet salt into a green one is brought about by repeatedly evaporating the aqueous solution in presence of hydrochloric acid and mercuric chloride; on extracting the residue with water, a green crystalline powder is left behind, which is composed of a double salt of the mercuric chloride and the green chloride.

A transmutation of a green dichloro-salt into a violet one may be brought about in the following way. When green dichloro-diethylenediamine chloride is warmed with ethylenediamine it gives a luteo-chloride, which, when heated to 150° C., loses a molecule of ethylene-diamine, and is converted into the violet dichloro-chloride:—

$$\underset{\text{Green dichloro-chloride.}}{\left[\mathrm{Cr}\begin{matrix}\mathrm{en}_2\\ \mathrm{Cl}_2\end{matrix}\right]\mathrm{Cl}} \xrightarrow{\text{en}} \underset{\text{Luteo-chloride.}}{\left[\mathrm{Cr\,en}_3\right]\mathrm{Cl}_3} \xrightarrow{150^{\circ}} \underset{\text{Violet dichloro-chloride.}}{\left[\mathrm{Cr}\begin{matrix}\mathrm{en}_2\\ \mathrm{Cl}_2\end{matrix}\right]\mathrm{Cl}}$$

Pfeiffer, in the following table, gives a synopsis of the transmutations he has obtained :—

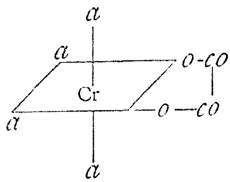


§ VI. *CONFIGURATION DETERMINATION.*

Pfeiffer employs the same method of determination as Werner used in the case of the cobaltamines' configuration, viz. the stability of certain ring compounds in the series of salts. The compounds which he has chosen for his experiments are the oxalato-diethylenediamine chromium salts :—

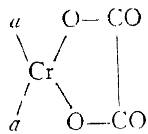
$$\left[Cr \begin{matrix} en_2 \\ \\ C_2O_4 \end{matrix} \right] X$$

The stable configuration of the complex radical within the bracket must be the following :—



The ethylene-diamine radicals are indicated here by *aa* instead of " en."

This, for the sake of simplicity, may be written in the form :—



in which one of the *a*-groups is supposed to lie above and one below the plane of the paper. These two groups are omitted from the figure for clearness.

If this position of the oxalato group be the true one (and the probability is much in its favour), then by replacing the oxalato group by two chlorine atoms we should be able to pass to what was undoubtedly a cis-dichloro-compound. And,

further, it should be more easy to pass from this dichloro-compound back into the oxalato salt than it would be if we set out from the isomeric dichloro-compound.

Experiment shows that when the oxalato salt is warmed with concentrated hydrochloric acid even to a temperature of 40° C., a violet salt is obtained, which, by double decomposition with potassium iodide, yields a crystalline iodide of the formula :—

$$\left[\mathrm{Cr}\begin{matrix}\mathrm{en_2}\\ \\ \mathrm{Cl_2}\end{matrix}\right]\mathrm{I}$$

which proves to be identical with the iodide of the violet salt series. As it was shown that under the conditions of the reaction no change of the green iodide into the violet one takes place, it seems certain that the violet salts are of an analogous configuration to the oxalato salt.

Again, the reverse change of the violet chloride into the oxalato salt is easily brought about by warming its solution with potassium oxalate, a complex salt being produced which has the constitution :—

$$\left[\mathrm{Cr}\begin{matrix}\mathrm{en_2}\\ \\ \mathrm{C_2O_4}\end{matrix}\right]\left[\mathrm{Cr}\begin{matrix}\mathrm{en}\\ \\ \mathrm{(C_2O_4)_2}\end{matrix}\right]$$

But when this reaction is carried out with the green chloride, a complex salt is formed which does not contain the group :—

$$\left[\mathrm{Cr}\begin{matrix}\mathrm{en_2}\\ \\ \mathrm{C_2O_4}\end{matrix}\right]$$

but, instead, the unchanged radical :—

$$\left[\mathrm{Cr}\begin{matrix}\mathrm{en_2}\\ \\ \mathrm{Cl_2}\end{matrix}\right]$$

The whole question depends upon the position of the oxalato group in the oxalato-diethylenediamine salts; and though no proof is possible of its real position, all the probability seems to favour of Pfeiffer's assumption.

SECTION II

STEREOCHEMICAL PROBLEMS INTO WHICH ISOMERISM DOES NOT ENTER

CHAPTER I.

THE PHENOMENA OF STERIC HINDRANCE.*

§ I.—*THEORETICAL.*

IN 1872, Hofmann[1] found that certain aromatic tertiary amines do not possess the property of uniting with alkyl iodides to form quaternary ammonium salts. Since then, many analogous cases have been observed by various workers, and an explanation of the phenomena has been put forward. The assumption is made that in any molecule each atom vibrates about a certain centre, and that the amplitude of this vibration is not negligible in comparison with the size of the molecule itself. It is obvious that, if this be granted, the atom will require for its motion a space in excess of its own volume. Now, if we suppose that another atom forces its way into the vibration sphere of the first atom, collisions between the two will occur, and it is probable that one or other will be driven back. The case is parallel to that of a person trying to force his way into a crowded room.

Now let us consider the application of this idea to the question

* This chapter contains a complete account of the most important researches in this branch of stereochemistry. Readers who are not interested in details are advised to omit § II. to § VIII. inclusive; § I. and § IX deal with the general principles of the subject.

[1] Hofmann, *Ber.*, 5, 704 (1872).

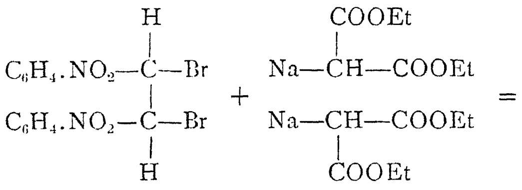
of chemical reactions. When two compounds react together, two groups are generally involved; for example, in the case of oxime formation the two groups are the :CO radical and the $-NH_2$ group. Obviously, these two will not react with one another until they come within range of each other's attractions; and if we can prevent their doing so, we shall be able to hinder the progress of the reaction. But this we should be able to do if we surrounded the carbonyl group with such a mass of atoms that the hydroxylamine molecule was unable to force its way in. This could be done by replacing the groups near the carbonyl by larger radicals. For example, if we replaced all the hydrogen atoms in acetone by methyl radicals we should expect to find that the reaction of oxime formation was very considerably impeded. This has been shown to be actually the case; and the name *Steric Hindrance* has been given to the phenomenon.

Bischoff[1] has put forward what is now generally known as his *Dynamic Hypothesis* by means of which he has been able to explain many peculiarities of reactions involving chain formation or intramolecular change. The Dynamic Hypothesis is based upon the assumption that in any molecule the atoms tend to take up positions which give the most scope for vibration; so that if a reaction can produce two end-products, the one formed in greatest amount will be that in which the atoms find the least hindrance to their motions within the molecule. Bischoff adopts the idea that the carbon chain is more or less cyclic in outline, and from this he deduces that the accumulation of substituents in the 1,5- or 1,6-position with regard to the groups concerned in any reaction will tend to hinder that reaction. The positions 1,5 and 1,6* are termed by Bischoff *critical positions*. An example of what is meant is furnished by the case of the reaction between dinitro-stilbene bromide and the sodium derivative of malonic ester. This reaction might be expected to take the course

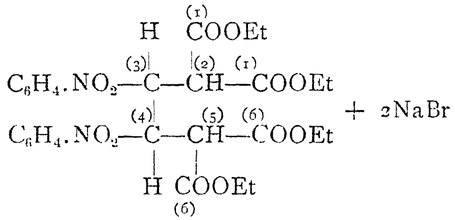
* Bischoff adopts the idea that the positions 1,5 or 1,6 in a carbon chain lie nearer together in space than 1,3 or 1,4. See following Chapters II. and IV.

[1] Bischoff, *Ber.*, **24**, 1087 (1891).

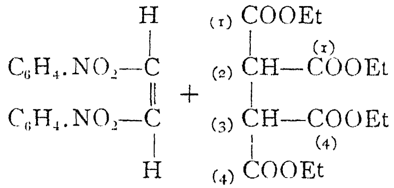
indicated in equation (I.), but, instead, it produces the compounds shown in (II.). It will be seen that if the product (I.) were actually formed, there would be four groups in the 1,6-position to one another, while this is not the case in (II.).



(I.)



(II.)



It is not necessary to quote any more examples in the present section, as many instances will be given later in this chapter.

The question of steric hindrance has been approached from another point of view. Measurements of the velocity of the addition of sodium hydrogen sulphite to various ketonic compounds showed that tautomeric compounds like acetoacetic ester had a greater reaction velocity than ordinary ketones such as acetone,[1] and this was explained by means of a new hypothesis.[2]

[1] Stewart, *Trans.*, **87**, 185 (1905); *Proc.*, **21**, 78 (1905).
[2] Stewart and Baly, *Trans.*, **89**, 489 (1906).

If we consider an ordinary solution of acetoacetic ester, evidently it is an equilibrium mixture of the two forms :—

$$\text{(I.) } CH_3.CO.CH_2.COOEt \quad \text{(II.) } CH_3.\underset{\substack{|\\ OH}}{C}:CH.COOEt$$

Now, when a molecule of the enolic form (II.) passes into the form (I.), the result is the formation of a carbonyl group from a hydroxyl group; and from analogy with the behaviour of atoms in the nascent condition we must suppose that this *nascent carbonyl group* is endowed with a much greater reactive power than is possessed by the ordinary non-nascent carbonyl radical, just as nascent hydrogen is distinguished from non-nascent hydrogen by its exceptional chemical activity. Stewart and Baly hold that the reactivity of any carbonyl group is not inherent in the group itself, but depends upon the "nascency" of the radical in question; the "nascency" being governed by the action of the adjacent groups upon the carbonyl radical. This implies that a process of vibration similar to that occurring in acetoacetic ester must be going on in the acetone molecule; and from spectroscopic evidence Stewart and Baly were able to prove that this was the case. They showed, further, that the reactivity of the carbonyl group in any compound is proportional to the persistence of a certain band in the absorption spectrum of the substance, so that the relative reactivities of two ketonic bodies can be approximately predicted without any actual measurements being necessary.

In the course of their investigations, Stewart and Baly found that in contradiction to the steric hindrance theory, the reactivity of the carbonyl radical in pyruvic ester was unexpectedly great; and the spectroscopic evidence gave grounds for supposing that in this compound also the reactivity is due to the formation of a nascent carbonyl group, which, however, is produced in a different manner from those previously mentioned, as it is brought into existence by the simple desmotropic change of (I.) into (II.) :—

$$\text{(I.) } \begin{array}{l} CH_3.C{=\!=}C{-}OEt \\ \,|\quad\;\; | \\ \,O{-}O \end{array} \qquad \text{(II.) } \begin{array}{l} CH_3.C{-}C{-}OEt \\ \,\|\quad \| \\ \,O\quad O \end{array}$$

Stewart and Baly have therefore rejected the hypothesis of steric hindrance in so far as it concerns such reactions as those of a carbonyl radical; and, instead, they attribute the hindering effects of substituents to the interference of these with the formation of the nascent carbonyl group. It is evident that if we substitute six methyl groups for the six hydrogen atoms of acetone there will be no chance of tautomeric change, and hence the carbonyl group is practically inactive.

The same theory has been applied to the case of the quinone oximes,[1] which at one time was supposed to be the classic instance of steric hindrance; and spectroscopic evidence proves conclusively that factors of much greater importance than steric hindrance are concerned in this case.*

Although, in these two instances, influences not allied to steric hindrance have been shown to play the chief rôle, many cases are known which have not yet been explained on any hypothesis other than that of steric hindrance; so that in the remainder of the present chapter it will be most convenient to deal with several problems and give explanations of them drawn from purely steric considerations, without laying great stress on the concomitant chemical questions which are involved.

§ II. *ESTERIFICATION.*

1. Aliphatic Acids.—It has long been known that the rate at which an ester is formed depends upon the constitution of the acid and alcohol which are employed. This question has been very fully investigated by Menschutkin,[2] who found that the rate of ester formation diminishes as the alcohol becomes

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* See p. 419.

[1] Stewart and Baly, *Trans.* **89**, 618, (1906).

[2] *Ann. Chim. Phys.*, [5] **20**, 229 (1880); **23**, 14 (1881); **30**, 81 (1883); *Jour. Russ. Phys. Chem. Soc.*, **9**, 316, 346 (1877); **10**, 278 (1878); **11**, 24, 345 (1779); **12**, 82 (1880); **13**, 564 (1881); **16**, 356 (1884); *Ber.* **13**, 1812 (1880); *Annalen*, **195**, 334 (1879); **197**, 193 (1879); *Trans.*, **89**, 1532 (1906).

more complicated in structure. Methyl alcohol reacts most rapidly; then in turn come higher primary, secondary, and tertiary alcohols; and it appears that an accumulation of radicals around the hydroxyl group of the alcohol exerts a hindering influence upon the reaction.

Hitherto, it has been usual to suppose that the hindrance was due to the fact that the radicals around the hydroxyl group shielded it from the action of the acid, as we have explained in the previous section. There is, however, another way in which the phenomenon may be treated. If we apply Bischoff's Dynamic Hypothesis to the present case, and take as an example the esterification of acetic acid with various alcohols, we should find compounds of the following types produced:—

(I.)

$$\overset{(1)}{CH_3}-\overset{(2)}{CO}-\overset{(3)}{O}-\overset{(4)}{CH_3}$$

(II.)

$$\overset{(1)}{CH_3}-\overset{(2)}{CO}-\overset{(3)}{O}-\overset{(4)}{CH_2}-\overset{(5)}{CH_3}$$

(III.)

$$\overset{(1)}{CH_3}-\overset{(2)}{CO}-\overset{(3)}{O}-\underset{\underset{CH_3}{(5)}}{\overset{(4)}{CH}}-\overset{(5)}{CH_3}$$

(IV.)

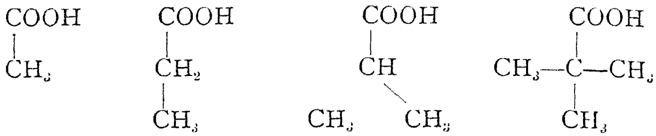
$$\overset{(1)}{CH_3}-\overset{(2)}{CO}-\overset{(3)}{O}-\underset{CH_{3\,(5)}}{\overset{CH_{3\,(5)}}{\overset{(4)}{C}}}-CH_{3\,(5)}$$

and it will be seen from an inspection of the formulæ that in Case I. no two atoms are in the critical 1,5-position to each other; in Case II., two atoms are thus placed, the methyl groups at the ends of the chain being in that position; in Case III., two methyl groups are in the 1,5-position to the methyl group in the acidic radical; while in the case of the tertiary alcohol, IV., there are three methyl groups in the 1,5-position to the methyl of the acid radical. Thus, on the Dynamic Hypothesis, there is an increasing hindrance to be expected as we pass from the lower to the higher alcohols.

The same hindrance is found when a series of acids various complexities is esterified with the same alcohol.

has been shown that, in the case of the substituted acetic acids, the rates of reaction decrease in the following order * :—

44·4% 41·2% 29·0% 8·3%



and in this case also, either of the two explanations may be advanced with equal justice.

Heyl and Victor Meyer[1] made a series of experiments of a similar nature, but since they were undertaken with a view to comparison with the aromatic acids, they will be dealt with later in this section.

Petersen[2] investigated the rates at which methyl esters were formed by various acids, and showed that in the case of isobutyric acid the velocity was only three-quarters of that obtained when normal butyric acid was used.

Sudborough and Lloyd[3] carried out a series of determinations of the velocity of esterification of various aliphatic acids. Their method was as follows: 100 c.c. of an N/5 solution of the acid were mixed with 100 c.c. of N/20 hydrochloric acid in ethyl alcohol solution, and kept at a proper temperature of 14·5° C. for a given time, at the end of which the amount of acid present in the solution was estimated by titration with N/20 sodium hydroxide. By using different times, the terms in the equation :—

$$K = \frac{1}{t} \log \frac{a}{a-x}$$

where a is the initial concentration of the acid, were obtained. Sudborough and Lloyd suggested that the letter E should be

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* These numbers represent the initial velocity or the percentage of acid (original amount = 100%) which is converted into ester when equi-molecular quantities of the acid and isobutyl alcohol are heated at 155° for an hour.

[1] Heyl and V. Meyer, *Ber.*, **28**, 188, 2776 (1895).

[2] Petersen, *Zeit. physikal. Chem.*, **16**, 385 (1895).

[3] Sudborough and Lloyd, *Trans.*, **75**, 467 (1899).

used to denote the esterification constant of an organic acid when normal hydrochloric acid is employed in ethyl alcohol solution. As the constant varies with the temperature and also with the alcohol used, they suggested also that expressions like $E^{15^\circ}_{MeOH}$ and $E^{15^\circ}_{EtOH}$ should be used to denote esterification constants for different alcohols at various temperatures. From the results obtained by Sudborough and Lloyd, it appears that the rate of esterification has no connection with the strength of the acid employed, as the following figures show:—

Acid.	Formula.	$E^{14\cdot5^\circ}_{EtOH}$	K [1]
Acetic . .	$CH_3.COOH$	3·661	0·00180
Propionic . .	$CH_3.CH_2.COOH$	3·049	0·00134
Isobutyric .	$(CH_3)_2 : CH.COOH$	1·0196	0·00144

These results differ from those of Lichty,[2] who used the autocatalytic method; for in his work he found that the amount of ester formed was proportional to the strength of the acid employed. It appears from this that in the one case the determining factor is the *strength* of the acid, while when hydrochloric acid is present the chief factor is the *constitution* of the acid. In a series of substituted acetic acids of the type:—

$$CH_2X.COOH \qquad CHX_2.COOH \qquad CX_3.COOH$$

it appears that the mono-substituted acid is more readily esterified than the di-, and this in turn more readily than the tri-substituted compound. This holds good, however, only if the radicals X are similar in each case; for it is found that trimethyl-acetic, for instance, esterifies much more easily than dichloracetic. The following figures give some illustration of the question:—

[1] Ostwald, *Zeit. physikal. Chem.*, **3**, 176 (1889)

[2] Lichty. *Amer Chem. J*, **17**, 27 (1895); **18**, 590 (1896).

Acid.	Formula.	$E^{14.5°}_{EtOH}$
Acetic	$CH_3.COOH$	3·661
Propionic	$CH_3.CH_2.COOH$	3·049
Isobutyric	$(CH_3)_2.CH.COOH$	1·0196
Trimethylacetic	$(CH_3)_3.C.COOH$	0·0909
Chloracetic	$Cl.CH_2.COOH$	2·432
Dichloracetic	$Cl_2.CH.COOH$	0·0640
Trichloracetic	$Cl_3.C.COOH$	0·0372
Phenylacetic	$C_6H_5.CH_2.COOH$	2·068
Diphenylacetic	$(C_6H_5)_2.CH.COOH$	0·05586

We must now examine the question of the unsaturated acids of the aliphatic series. Sudborough and Lloyd[1] examined the behaviour of about thirty derivatives of acrylic acid, and from their results certain conclusions may be drawn.

Di-substituted acrylic acids, (I.), in which one substituent is in the α-position and the other in the trans-position with regard to the carboxyl, are readily esterified when boiled for an hour with a 3% solution of hydrochloric acid :—

$$\text{(I.)}\quad \begin{array}{l} \text{Y—C—H} \\ \quad\;\, \| \\ \text{X—C—COOH} \end{array}$$

but if the substituent Y be transferred to the cis-position, as in (II.), the acid becomes difficult to esterify :—

$$\text{(II.)}\quad \begin{array}{l} \text{H—C—Y} \\ \quad\;\, \| \\ \text{X—C—COOH} \end{array}$$

The same is found when in (I.) a third substituent is introduced in place of the hydrogen atom, for compounds of the type (III.) are also difficult to esterify :—

$$\text{(III.)}\quad \begin{array}{l} \text{Y—C—Z} \\ \quad\;\, \| \\ \text{X—C—COOH} \end{array}$$

[1] Sudborough and Lloyd, *Trans.*, **73**, 81 (1898).

The hindering influence of the two groups in the β-position, however, is only marked when a substituent is present in the α-position; for compounds of the type (IV.) are easily esterified:—

$$\text{(IV.)}\quad \begin{array}{l} \text{Y—C—Z} \\ \quad\;\; \| \\ \text{H—C—COOH} \end{array}$$

It appears that the weights or volumes of the radicals in the α- and cis-positions have considerable influence upon the amounts of esters formed by the substituted acids. This is clearly shown in the cases of the halogen-substituted cinnamic acids, for which the figures are given below:—

Cinnamic acid.	M.P.	Per cent. ester formed.
Dichloro-	120°	30·90 and 30·34
Dibromo-	139°	7·92 ,, 8·19
,, ...	100°	13·38 ,, 13·13
Di-iodo-	170°	2·10 ,, 1·96

Sudborough and Roberts [1] carried out further investigations in the same series of acids, and were able to confirm the work which had been done previously. They investigated the relations between the esterification constants of the unsaturated acids and those of the saturated analogues; and showed that the saturated acid is much more readily esterified than the corresponding unsaturated compound:—

Unsaturated.	E.	Saturated.	E.
Crotonic	1·28	Butyric	41·63
Cinnamic	0·937	Hydro-cinnamic . .	43·20
Fumaric mono-ethyl ester	1·79 }	Succinic mono-ethyl ester	17·25
Maleic mono-ethyl ester .	0·859 }		

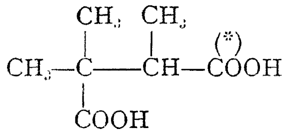
This may imply that the atoms are more closely grouped

[1] Sudborough and Roberts, *Trans.*, **87**, 1840 (1905).

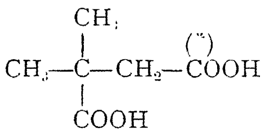
together in the unsaturated compound than in the saturated one: but there is no proof that this is the case.

The series of aliphatic dicarboxylic acids must now be examined.

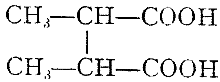
Anschutz[1] pointed out that when a dicarboxylic acid is esterified by means of alcohol and hydrochloric acid, the velocity of esterification will be influenced by the presence of substituents; and that it is probable that a carboxyl group united with a tertiary carbon atom will be esterified more easily than one which is joined to a quaternary carbon atom. That is to say, in the compound shown below, the carboxyl group which has an asterisk attached to it will be esterified before the other:—



Blaise[2] examined the somewhat similar case of dimethyl-succinic acid, and showed that in this case the carboxyl with the asterisk was much more readily esterified than the other.



(I.)



(II.)

He showed, further, that when a symmetrically substituted succinic acid, (II.), was esterified, the proportion of acid to neutral ester was less than in the case of the unsymmetrical acid (I.); which is another way of expressing the same result. The substituted glutaric acids gave similar results.

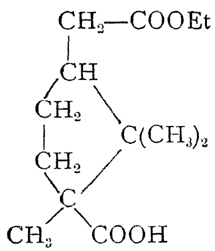
[1] Anschutz, *Ber.*, **30**, 2652 (1897).

[2] Blaise, *Compt. rend.*, **126**, 753 (1898); **128**, 676 (1898).

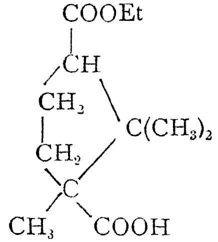
Piutti [1] showed that when aspartic acid was esterified it yielded the β-ester $COOH.CH(NH_2).CH_2.COOR$. From this it may be concluded that the amido group in the α-position has some influence upon the esterification process.

2. Alicyclic Acids.—The only substances which need be mentioned in this section are hydromellitic, camphoric, and hydroxycampho-carboxylic acid.

Haller [2] showed that when homocamphoric acid was treated with hydrochloric acid and alcohol it gave very little neutral ester, the chief product being an acid ester having the following formula :—



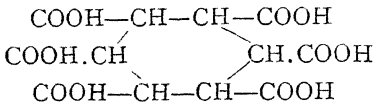
Haller,[3] as well as Bruhl and Braunschweig,[4] have proved that the same occurs in the case of camphoric acid itself, as, when similarly treated, it also gives an acid ester of the formula :—



[1] Piutti, *Gazzetta*, **17**, 126, 457 (1887).
[2] Haller, *Compt. rend.*, **109**, 68, 112 (1889).
[3] Haller, *Ibid.*, **114**, 1516 (1892).
[4] Bruhl and Braunschweig, *Ber.*, **25**, 1796 (1892).

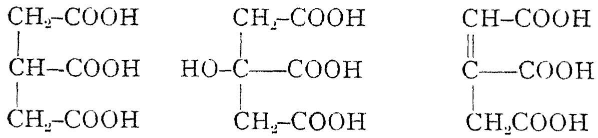
The isomeric esters, in which the ethyl is attached to the other carboxyl group, are obtained by first preparing the diethyl ester of the acid, and then submitting it to a process of partial hydrolysis. In this way it is found that the group which is most easily esterified is also the most easily hydrolysed.

The case of hydromellitic acid



is even more remarkable, as in this case, though there are six carboxyl groups in the molecule, not one of them is esterified by the usual method with hydrochloric acid and alcohol. In the case of the isomeric isohydromellitic acid, one carboxyl group can be esterified by this process. This behaviour is not due to the mere presence of the carboxyl groups attached to neighbouring carbon atoms, as it is found that tricarballylic acid (I.), citric acid (II.), and aconitic acid (III.), all give tri-esters under the same conditions as those under which hydromellitic acid fails to react :—

(I.) (II.) (III.)



Tricarballylic Acid. Citric Acid. Aconitic Acid.

The explanation cannot rest upon chemical grounds, and it seems best to adopt the view put forward by van Loon[1]—that the two hydromellitic acids differ in the arrangement of their carboxyl groups in space, so that in the case of hydromellitic acid itself we have the formula (I.), while in the case of isohydromellitic acid the substance has the configuration (II.) :—

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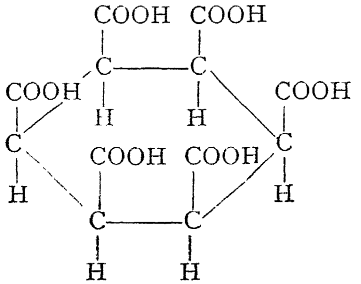
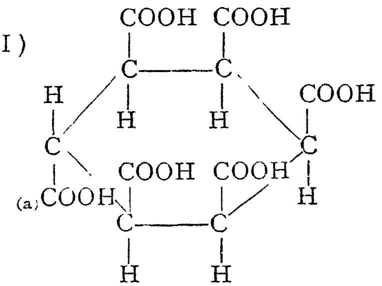
[1] Van Loon, *Ber*, **28**, 1272 (1895).

(I.)



(II)

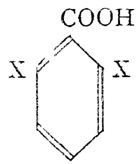


In the case of (I.) there would be very little chance of the alcohol molecules approaching any single carboxyl group, as the vibrations of the two neighbouring carboxyls would tend to drive them away; but in the case of (II.), one of the carboxyl radicals, (a), being on the side of the ring opposite to the rest, is free from this hindering influence, and would therefore be capable of esterification.

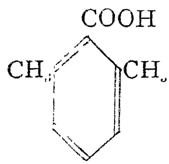
3. Aromatic Acids.—In this series of compounds the effect of spacial influences upon the course of the esterification process has been studied much more fully than in the analogous case of the aliphatic series; and it may be said that the behaviour of the substituted benzoic acids furnishes the most conclusive demonstration of the correctness of the hypothesis of steric hindrance. The greatest worker in this field has been the late Victor Meyer,[1] who first observed the phenomenon in the benzoic acid series.

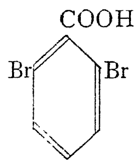
[1] V. Meyer, *Ber.*, **27**, 510 (1894); **28**, 182, 1254, 1798, 2773, 3197

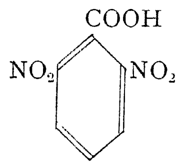
It was shown by him that when a carboxyl group lay in the benzene ring between two ortho-substituents :—



its volocity of esterification under certain conditions was very considerably diminished. For instance, if benzoic acid or any homologue which is not of the above structure be dissolved in methyl alcohol, cooled with water, saturated with hydrochloric acid gas, and allowed to stand for twelve hours at the same temperature, about 90 per cent. of ester is formed. The same result is obtained if the acid be heated for three hours under a reflux condenser with a 3 per cent. solution of hydrochloric acid gas in methyl alcohol. But if, on the other hand, the same experiment be tried with a diortho-substituted benzoic acid, such as :—







the acid is very slightly esterified. Even when only one ortho-substituent is present this hindering influence is noticeable. From these and many similar cases, Victor Meyer deduced what has since been known as his *Esterification Law*, which is enunciated as follows: "*When in any substituted benzoic acid the two hydrogen atoms in the ortho-positions to the carboxyl group are replaced by atoms or radicals such as chlorine, bromine, methyl, or carboxyl, an acid is produced which*

(1895); **29**, 831, 1399, 1401 (1896); *Zeit. physikal. Chem.*, **24**, 219 (1897); V. Meyer and Sudborough, *Ber.*, **27**, 1580, 3146 (1894); van Loon and V. Meyer, *Ibid.*, **29**, 839 (1896); V. Meyer and Wohler, *Ibid.*, **29**, 2569 (1896); V. Meyer and Molz., *Ibid.*, **30**, 1277 (1898).

can be esterified by means of hydrochloric acid and alcohol only with great difficulty."

We must now deal with the material which has been accumulated by various workers on this branch of the subject, and in order to facilitate the exposition we shall arrange the matter under three heads—mono-basic acids, di-basic acids, and polybasic acids.

The first series of acids with which we need concern ourselves are the mono-methyl substituted benzoic acids. Victor Meyer and Kellas[1] made a very full examination of the velocity of esterification in the case of these acids, using the following method. Half a gramme of the acid was dissolved in fifty grammes of freshly distilled methyl alcohol containing two per cent. of hydrochloric acid; the mixture was kept for two hours in a thermostat at a given temperature, after which the amount of ester formed was estimated. The table below gives the results which were thus obtained :—

Acid.	Temp. 0°.	17°	31°	40°	51°
Benzoic . .	8·4	21·8	37·0	59·3	82·5
o-Toluic . .	7·8	11·2	18·1	27·1	48·3
m-Toluic . .	8·7	20·0	42·2	59·4	77·1
p-Toluic . .	8·9	18·4	39·1	55·3	75·6

Analogous results were obtained by Goldschmidt[2] and Petersen.[3] It was shown in the case of the aliphatic acids that the esterification constant had no apparent connection with the dissociation constant of the acid employed; and the same holds good in the aromatic series also, as can be seen by comparing the dissociation constants of these four acids with the foregoing figures :—

	K
Benzoic acid	0·00600
o–Toluic acid	0·01200
m–Toluic acid	0·00514
p–Toluic acid	0·00515

[1] V. Meyer and Kellas, *Zeit. physikal Chem.*, **24**, 219 (1897)
[2] Goldschmidt, *Ber.*, **28**, 3218 (1895).
[3] Petersen, *Zeit. physikal. Chem.*, **16**, 385 (1895)

The influence of the methyl group in the ortho-position is very strongly marked in comparison with the effect of the same group in either the meta- or para-position. We may now compare these results with some obtained when other substituents are used instead of methyl radicals, as in this way it should be possible to gain some insight into the cause of the hindrance. The following table is taken from the work of Victor Meyer and Kellas:—

Acid.	Temp 0°.	17°	31°	40°	51°	35°
Chlorobenzoic *o*-	4·8	11·4	20·8	30·2	50·9	
,, *m*-	10·7	16·1	31·5	48·6	72·0	
,, *p*-	8·3	14·0	27·8	44·8	70·5	
Bromobenzoic *o*-	3·2	8·4	14·6	22·9	43·4	
,, *m*-	8·8	15·3	27·6	44·2	66·6	
,, *p*-	7·4	13·8	23·6	41·4	61·0	
Iodobenzoic *o*-	—	6·9	9·7	14·6	20·5	
,, *m*-	—	14·5	26·2	39·7	57·6	
,, *p*-	—	13·5	23·3	36·4	52·9	
Nitrobenzoic *o*-	2·5	4·0	5·6	7·0	8·6	
,, *m*-	9·9	13·3	25·2	37·6	57·1	
,, *p*-	9·1	13·3	25·2	37·0	57·1	
Hydroxybenzoic *o*-	—	—	—	—	—	15·27
,, *m*-	—	—	—	—	—	55·97
,, *p*-	—	—	—	—	—	51·33

When we examine the above figures in detail, we find that from them we may draw the following conclusions. In the case of ortho-substituents, the effects increase in the order—chlorine or methyl, bromine, iodine, and the nitro-group. It is obvious that if we are to consider the effect of spacial influences, we must choose the ortho-substituent as the test case, for it must be supposed to lie nearer to the carboxyl group than either the meta- or the para-substituent does. Further, if we adopt the steric view, it is clear that the weight of the substituent will influence the reaction; as was pointed out in the introductory section, if the alcohol molecule can be driven back before it has time to react with the carboxyl radical, no ester will be formed; and if the inertia of the substituents in the neighbourhood of the carboxyl group is great, this expulsion of the alcohol molecule is likely to be more rapid than would be the

case if they were light radicals, which could be easily pushed aside. Now, to test this, we have only to compare the relations between the atomic weights of the atoms in the ortho-position to the carboxyl with their actions upon the esterification process. Writing the substituents in the order ascertained from the table, and putting under each the relative weight of the substituting group,* we obtain the following:—

CH_3	Cl	Br	I	NO_2
15	35·5	80	127	46

Thus the only result which does not agree with the steric view is that obtained with nitro-benzoic acid. Now, it has been shown by Baly and Collie[1] that the introduction of the nitro-group into the ring brings about a complete change in the vibration of the benzene molecule; so, if the results obtained in the case of the halogens can be supported by other evidence, we should be justified in laying comparatively little stress on the anomalous behaviour of the nitro-compounds. We must now show how this new evidence was obtained.

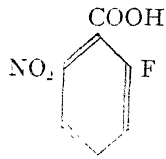
The strongest objection which can be brought against the steric view of these hindrances lies in the fact that they may be supposed to be due to the purely chemical influences brought into play by the presence of the halogen atoms in the ortho-position to the carboxyl group. If we can show that a strongly electro-negative group of light atomic weight exerts less hindering influence than a weaker electro-negative group of heavier weight, it will be almost certain proof that the steric factor in the question outweighs the purely chemical one. The problem was approached by van Loon and Victor Meyer[2] in the following way. It was known that diortho-substituted acids differed very much in their velocity of esterification; for when a stream of hydrochloric acid gas is led into a boiling alcoholic solution of a dimethyl-benzoic acid of this type, it is almost completely esterified in a short time; whereas, under

* Of course, this is merely a rough method for the sake of illustration. The atomic volumes are also factors in the problem.

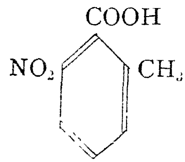
[1] Baly and Collie, *Trans.*, **87**, 1332 (1905).

[2] van Loon and V. Meyer, *Ber.*, **29**, 839 (1896).

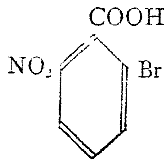
the same conditions, a dinitro-, dibromo-, or dichloro-acid is hardly esterified at all. Fluorine being more strongly electro-negative than chlorine, while having a lower atomic weight, it was chosen for a test substance. It was found that the behaviour of diortho-nitro-fluoro-benzoic acid, (I.), showed a closer resemblance to that of diortho-methyl-nitro-benzoic acid, (II.), than to that of diortho-bromo-nitro- or diortho-iodo-nitro-benzoic acid, (III.) and (IV.) :—



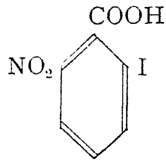
(I.)



(II.)



(III.)



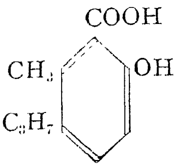
(IV.)

Thus it appears a probable deduction that the spacial influence overpowers the chemical influence in this case; for if it did not we should expect to find the fluorine compound ranging itself along with those of bromine and iodine, to which it has a close chemical likeness.

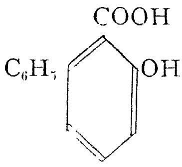
It is unnecessary to enter into a description of every case which has been observed, as many of them have no great theoretical importance. Reference may be made to papers by Beilstein and Kuhlberg,[1] Salkowsky,[2] Kretzer,[3] Graebe and Gourevitz,[4] Jakobsen[5] and Cohen.[6]

[1] Beilstein and Kuhlberg, *Annalen*, **152**, 237 (1869).
[2] Salkowsky, *Ibid.*, **163**, 32 (1872).
[3] Kretzer, *Ber.*, **30**, 1946 (1897)
[4] Graebe and Gourevitz, *Ibid.*, **33**, 2025 (1900).
[5] Jakobsen, *Ibid.*, **22**, 1221 (1889)
[6] Cohen, *Trans.*, **89**, 1482 (1906).

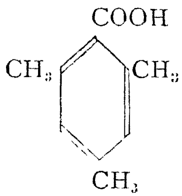
We may examine the cases of those substituent groups which we have hitherto left undescribed. First among these is the hydroxyl radical.



(I.)



(II.)

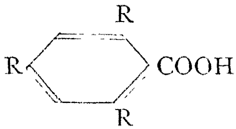


(III.)

The cases of thymotic acid, (I.), and ortho-phenylsalicylic acid, (II.), have been dealt with by Victor Meyer and Sudborough,[1] who found the following results. The results for mesitylenic acid, (III.), obtained under the same conditions (heating on a water-bath for five hours), are given for the sake of comparison :—

Acid.	Per cent. ester formed.
Thymotic (I.)	23·3
o-Phenylsalicylic (II.)	76·5
Mesitylenic (III.)	64·5

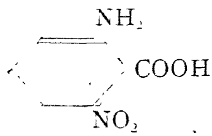
It is evident that the hydroxyl group does not exert a very powerful hindering influence; though it seems much stronger than methyl, for, under these conditions, acids of the type :—



(where R is Cl, Br, or NO_2) give no ester at all.

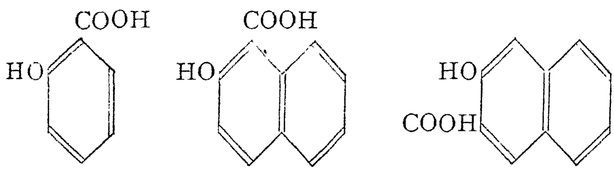
[1] V. Meyer and Sudborough, *Ber.*, **27**, 1580 (1894) ; V. Meyer, *Ibid.*, **28**, 182, 1262 (1895).

The influence of the amido group appears to be strong, for Kahn[1] found that 2-nitro-6-amidobenzene-1-carboxylic acid:—



could not be esterified by an alcoholic hydrochloric acid solution. This may, however, be due to the chemical nature of the amido radical.

The second benzene ring in the naphthalene compounds appears to exert a hindering influence on the esterification process of some acids.



(I.) (II.) (III.)

For instance, Victor Meyer and Sudborough[2] showed that the percentage amounts of methyl ester formed in eight hours by salicylic acid, (I.), β-hydroxy-α-naphthoic, (II.), and β-hydroxy-β-naphthoic acid, (III.), for various temperatures were as follows:—

Acid.	Temp. 0°.	20°	40°	60°
Salicylic (I.)	9–10	33–4	81–2	98
β-Hydroxy-α-naphthoic (II.) .	0	3	26	63·5
β-Hydroxy-β-naphthoic (III.) .	90% at ordinary temperatures			

In the following cases,[3] (1), (2), and (3) form no ester at all,

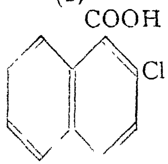
[1] Kahn, *Ber.*, **35**, 3864 (1902).

[2] V. Meyer and Sudborough, *Ibid.*, **27**, 1580 (1894); V. Meyer, *Ibid.*, **28**, 182 (1895).

[3] V. Meyer, *Ibid.*, **28**, 182 (1895).

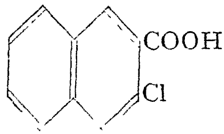
while the isomeric acids (1A), (2A), and (3A) give a 90 per cent. yield under the same conditions :—

(1)



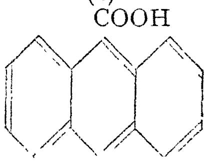
β-Chloro-α-naphthoic acid.

(1A)



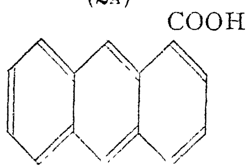
β-Chloro-β-naphthoic acid.

(2)



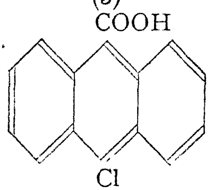
γ-Anthracene carboxylic acid.

(2A)



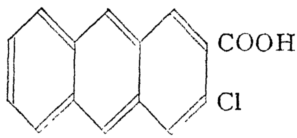
α-Anthracene carboxylic acid.

(3)



γ-γ-Chloro-anthracene carboxylic acid.

(3A)



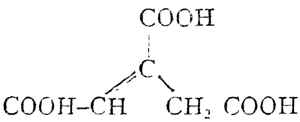
β-β-Chloro-anthracene carboxylic acid.

In concluding the survey of the aromatic mono-carboxylic acids, reference may be made to the views advanced by Victor Meyer.[1] According to him, if the arrangement of atoms in open-chain compounds resembled that of cyclic substances, then acids of the type :—

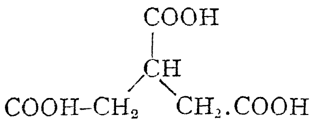
$$\begin{array}{l} CR_2 \\ \quad \backslash\backslash \\ \quad\; C{-}COOH \\ \quad / \\ CR_2 \end{array}$$

[1] V. Meyer, *Ber.*, **28**, 188 (1895).

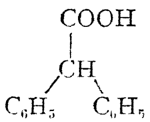
should give esters only with considerable difficulty, since their structure resembles that of the diortho-substituted aromatic acids. Heyl and Victor Meyer[1] examined the behaviour of the four acids shown below, but found that in none of them was there any hindrance noticeable :—



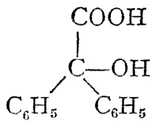
Aconitic acid.



Tricarballylic acid.

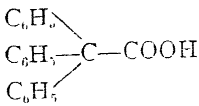


Diphenylacetic acid.

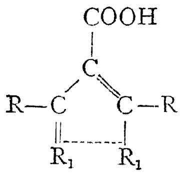


Benzilic acid.

Triphenyl-acetic acid, however, gave only twenty per cent. of ester under conditions which gave quantitative yields with the other acids :—



It seems clear that the configurations of the aliphatic and aromatic substances are not similar, but too much stress must not be laid upon an incomplete proof of this type. It can be seen by comparison that not one of the above formulæ (with possibly the exception of triphenyl-acetic acid) resembles the true aromatic type :—



[1] Heyl and V. Meyer, *Ber.*, **28**, 2776 (1895).

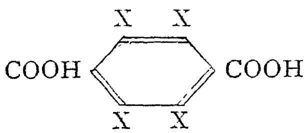
in which no hydrogen atoms are attached to the three carbon atoms of the ring.

Passing now to the series of aromatic dicarboxylic acids, we find that similar influences seem to govern their esterification. In the first place, we shall deal with those acids which have not two carboxyl groups in the ortho-position to one another.

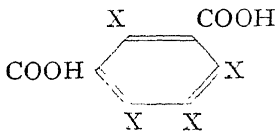
It has been shown by Victor Meyer[1] and Rupp[2] that the following acids, when heated with an alcoholic 3 per cent. solution of hydrochloric acid, give no esters :—

Tetrachloro-terephthalic acid,
Tetrabromo-terephthalic acid,
Tetra-iodo-terephthalic acid,
Tetrachloro-isophthalic acid,
Tetrabromo-isophthalic acid,
Tetra-iodo-isophthalic acid.

That is to say, that acids of type (I.) or type (II.) conform to Victor Meyer's Esterification Law :—



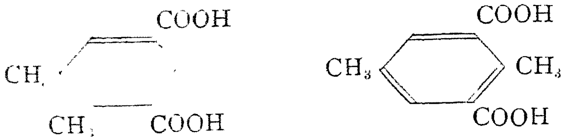
(I.)



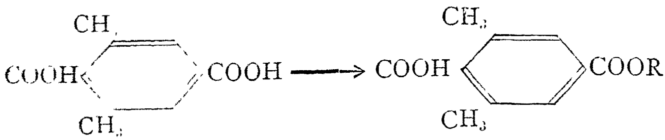
(II.)

When a dicarboxylic acid has one carboxyl group situated between two substituents, while the other is free from ortho-substituents, the second carboxyl group is esterified, and an acid ester is thus formed. For instance, Jannasch and Weiler[3] observed the following behaviour in the case of three acids :—

[1] V. Meyer, *Ber.*, **28**, 3197 (1895).
[2] Rupp, *Ibid.*, **29**, 1625 (1896)
[3] Jannasch and Weiler, *Ibid.*, **28**, 531 (1895).

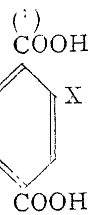


Give neutral esters.



Gives the acid ester.

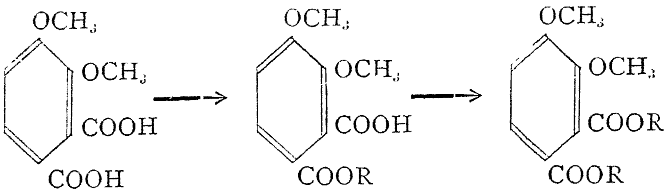
Similar behaviour has been noticed in nitro-terephthalic acid,[1] bromo-terephthalic acid, and hydroxy-terephthalic acid,[2] for in this case the carboxyl group marked with an asterisk is esterified before the other :—



When the two carboxyl groups are in the ortho-position to one another, the results become more complicated ; and no great reliance can be laid upon them from the stereochemical point of view. We may content ourselves with a review of several cases, beginning with hemipic acid, (I.), which has been studied by Wegscheider.[3] He found that the first substance formed was the acid ester, (II.), which on longer treatment was converted into the neutral ester, (III.) :—

---

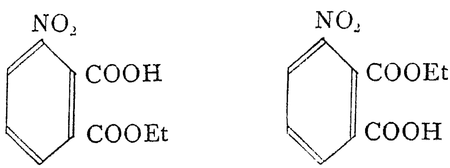
[1] Wegscheider, *Monatsh.*, **21**, 621 (1900) ; **23**, 405 (1902).
[2] Wegscheider and Bittner, *Ibid.*, **21**, 638 (1900).
[3] Wegscheider, *Ibid.*, **16**, 137 (1895).



Hemipic acid. (I.) Acid ester. (II.) Neutral ester. (III.)

From this we might conclude that Victor Meyer's Law held good in the case of the phthalic acids also ; since in this case the carboxyl group, having only one ortho-substituent, has been attacked before the second carboxyl group which lies between two substituents.

When we come to the case of 3-nitrophthalic acid, however, we find that this rule only holds good under certain conditions ; for McKenzie [1] has shown that when this acid is esterified with amyl alcohol the ester (1) is formed, while when the anhydride is used instead of the acid, the ester produced in greatest quantity has the formula (2) :—



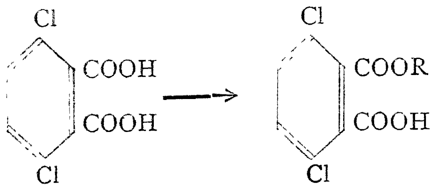
3-Nitrophthalic esters.

(1) (2)

Graebe [2] found that when 3,6-dichlorophthalic acid, (A), was allowed to stand for twelve hours with alcoholic hydrochloric acid it yielded an acid ester, (B), which on further standing, or even on heating, was not converted to any extent into a neutral ester. This seems to point to the possibility of

[1] McKenzie, *Trans.*, **79**, 1135 (1901).
[2] Graebe, *Ber.*, **33**, 2019 (1900).

an esterified carboxyl group exercising a greater hindering effect than a simple carboxyl radical :—



3,6-Dichlorophthalic acid. (A) Acid ester. (B)

The tetrahalogen-substituted phthalic acids [1] show a similar behaviour.

Having now reviewed the mono- and di-carboxylic acids of the aromatic series, we must give a few details concerning the poly-basic acids. As has been shown in the case of the ortho-phthalic acids, the hindering effect of the carboxyl group is not great, and we might therefore expect to find some exceptions to the esterification law in this series.

The following tri-carboxylic acids have been examined: trimesic acid, (I.), gives a neutral ester; [2] hemimellitic acid, (II.), gives a di-ester under ordinary conditions, [3] and only a trace of neutral ester when heated. [4] This is another instance of the hindrance which alkylated carboxyl groups offer to the esterification of carboxyls in the ortho-position to them. Here the influence seems to be as strong as if the ortho-substituents were bromine atoms instead of ester groups, which is quite different from the behaviour of the non-esterified carboxyl radical :—

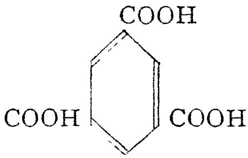
---

[1] Graebe, *Annalen*, **238**, 327 (1887); V. Meyer, *Ber.*, **28**, 182 (1895).

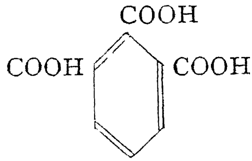
[2] Fittig and Furtenbach, *Annalen*, **147**, 309 (1868); V. Meyer and Sudborough, *Ber.*, **27**, 1590 (1894); **29**, 840 (1896).

[3] Graebe and Leonhardt, *Annalen*, **290**, 217 (1896); V. Meyer and Sudborough, *Ber.*, **27**, 1590; **29**, 840 (1896).

[4] V. Meyer, *Ber.*, **29**, 1401 (1896).



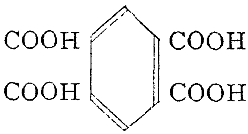
(I.)
Trimesic acid.



(II.)
Hemimellitic acid.

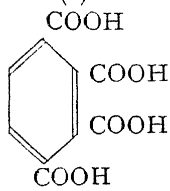
As regards the tetra-carboxylic acids, the results from the steric point of view are even more confusing. Pyromellitic acid,[1] (1), gives even in the cold 90% of ester; under the same conditions, the isomeric prehnitic acid,[2] (2), gives an acid di-ester, (3), but when this is esterified at the boiling-point of alcohol it yields the neutral ester, (4). So that in this case the results differ completely from those obtained with the tri-carboxylic acids:—

(1)

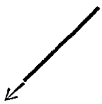


Pyromellitic acid.

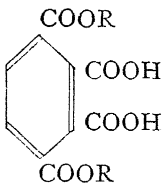
(2)



Prehnitic acid.

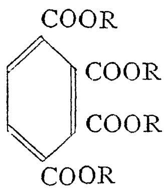


(3)



Prehnitic di-ester.

(4)

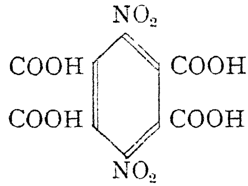


Prehnitic tetra-ester.

Dinitro-pyromellitic acid[3] is extremely hard to esterify, for

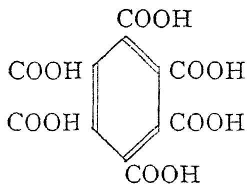
[1] V. Meyer and Sudborough, *Ber.*, **29**, 840 (1896).
[2] V. Meyer and Sudborough, *Ibid.*, **27**, 1590 (1894).
[3] Nef, *Annalen*, **237**, 22 (1887).

even after being heated for two days with alcohol and a drop of sulphuric acid it forms merely a trace of ester. This, again, is in direct contradiction to the facts quoted in the last paragraph.



Dinitro-pyromellitic acid.

Mellitic acid[1] itself does not appear to form any ester.



Mellitic acid.

4. The Theory and Application of the Esterification Law.—In the foregoing pages we have given an account of the experimental results arrived at during the past ten years, and we must now discuss the deductions which have been drawn from this extensive material.

In the first place, we may leave out of account the aliphatic substances, as these will be dealt with from a different point of view in the section of this chapter which deals with Chain Formation. Under that head, a very great quantity of experimental work has been collected; and from it we can draw more definite conclusions than can be deduced from the more restricted material which we have summarised in the present section. We are therefore left with the aromatic acids and their esters.

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[1] Wohler and Schwarz: *Annalen*, **66**, 49.

The problem which must be dealt with first is that of the relative effects produced by the same substituent when it is introduced into the three possible positions with regard to the carboxyl radical. As can be seen from an inspection of the table on p. 330, the ortho-substituent has by far the greatest influence upon the course of the esterification process. This is, of course, what would be anticipated from the steric hypothesis. On the other hand, the meta-substituent appears to have less effect than a similar radical in the para-position. In the case of these two types, therefore, we can gain but little information which will be of use in the development of stereochemical conceptions; the known close relation between the para-positions in the benzene ring seems to point to the difference between the influence of substituents in the para- and in the meta-positions being due to some chemical rather than stereochemical cause. If stereochemical theories are to be introduced at all, it seems probable that the views as to the vibrations of the benzene ring put forward by Baly, Edwards, and Stewart,* offer suggestions as to the lines along which the question must be approached. There seems, however, no reason for insisting upon a stereochemical explanation.

We must now examine the case of the ortho-substituent in order to see if it can be shown that the spacial factor in the problem is really the preponderant one. We have already proved by the example of nitro-fluoro-benzoic acid that the stereochemical influence may be greater than a purely chemical one; but in order to furnish conclusive proof we should show that, if the carboxyl group be removed in space from the sphere of action of the substituents, it will regain its original capacity for ester formation. Though we cannot actually remove the carboxyl group further from the benzene ring than its normal distance without altering the whole molecule, still we can achieve a very similar result by interpolating a methylene group between the ring and the carboxyl radical. By this means we are able to project the carboxyl beyond the range of the hindering influence of the substituents. When this is done, we

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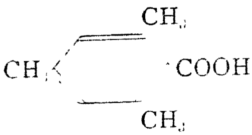
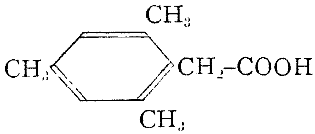
* See Chapter V. of this Section.

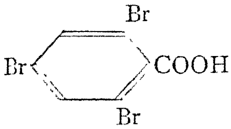
should expect a marked rise in the amount of ester formed by the new compound when compared with the original one. This has actually been found to be the case, as the following figures show :—



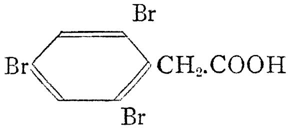
Mesityl-formic acid.
Gives no ester.



Mesityl-acetic acid.
Gives 96 per cent. of ester.



Tribromobenzoic acid.
Gives no ester.



Tribromophenyl-acetic acid.
Gives 98·8 per cent. of ester.

These are not isolated examples, as many similar ones are known. It may be pointed out, however, that this is not a rigorous proof of the theory ; for it is quite conceivable that the difference in the esterification velocities is brought about by the changes in structure, and not by changes in the space relations between the atoms. This question, in the present state of our knowledge, must remain unsettled.

Another method of applying the same idea is the following. If we could attach to the carboxyl some heavy atom whose mass would be so great that its collisions with the groups in the ortho-positions during its vibrations would be sufficient to drive the substituents back, and thus open a way for the alkyl radical to enter, we should expect to find a very great increase in the rapidity of esterification. Such an atom is easily found, for the silver atom has an atomic weight much greater than that of any ordinary substituent atom ; and it has, further, the property of reacting easily with alkyl iodides. If we substitute the reaction between a silver salt and an alkyl iodide for one between an acid and an alcohol, we should therefore expect to find a very marked increase in the yield of ester produced.

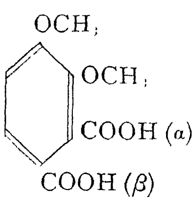
'his actually proves to be the case, for many acids which annot otherwise be esterified can be converted into their steis by means of this method. This also, however, is not rigorous proof, as will be shown in the discussion of the iechanism of the reaction of esterification by means of hydro-iloric acid, with which we are about to deal.

Four chief hypotheses have been put forward for this iechanism.

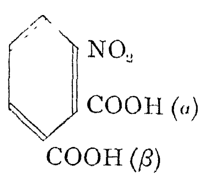
In the first place, the esterification process may be onsidered to be an ordinary ionic reaction; and may be ipposed to take place in accordance with the equation :—

$$R.COO' + H^{\cdot} + HO.R_1 = R.COOR_1 + H_2O$$

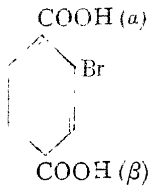
this were actually the case, the acid with the greatest affinity onstant would react more easily than its weaker analogues; hich, as we have shown, has not been observed. Again, has been shown that the ieaction between an alkyl iodide id the silver salt of an acid is an ordinary ionic one; and it ies not appear to be influenced by spacial conditions at all. has been usual to distinguish between the two reactions the assumption that the silver salt reaction proceeds in-intaneously, while the esterification with hydrochloric acid a comparatively slow process. Further, if these two reactions ere of a similar type, they should both yield the same end-oduct when applied to the same acid and alcohol. This is t the case, as can be seen from the example of the following carboxylic acids. It is found that when the silver salt ethod is used, and the acid salt is employed, the carboxyl (α), iich has the greater affinity constant, is the one which comes esterified; while when hydiochloric acid and alcohol used, the weaker (β) radical is attacked .—



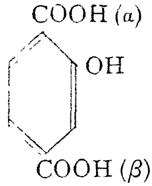
Hemipic acid.



3-Nitrophthalic acid.



Bromo-terephthalic acid.



Hydroxy-terephthalic acid.

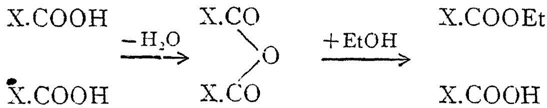
We may therefore fairly deduce that the esterification process is not an ionic reaction; though it is quite possible that ionic relations may have a certain influence upon it.

A second view of the mechanism of ester formation regards it as a reversible reaction of the type :—

$$X.COOH + Y.OH \rightleftharpoons X.COOY + H_2O$$

On this hypothesis, those cases in which small yields of ester are obtained are explained by supposing that, in presence of water, the back reaction of hydrolysis becomes practically equal in velocity to the forward reaction of ester formation. Goldschmidt[1] tested this in the following manner. Symmetrical trinitrobenzoic acid is very hard to esterify by means of alcohol and hydrochloric acid; it should therefore be easy to hydrolyse its ester under the same conditions. Goldschmidt prepared the ethyl ester from the silver salt, dissolved it in alcoholic hydrochloric acid to which a little water had been added, and left it in a thermostat at 25° C. for four weeks. At the end of this time the alcohol had all evaporated; and crystals remained behind, which, on examination, proved to be merely the original ester. No considerable hydrolysis had taken place. It appears from this that the explanation of hindrance, based upon the rapid hydrolysis of the ester as soon as it is formed, cannot be maintained.

A third view of esterification assumes that an anhydride is first formed, which is then attacked by the alcohol. Thus :—



[1] Goldschmidt, *Ber.*, **28**, 3218 (1895).

In the series of monobasic acids, this process must take place between two molecules of the acid, and it would then be subject to steric hindrance from the accumulation of substituents in the alkyl radical attached to the carboxyl group. In this case, then, the theory agrees with the facts. But, on the other hand, if we take an aromatic monobasic acid, its anhydride formation would be hindered in the same way by a substituent in the ortho-position to the carboxyl group; but the introduction of a second carboxyl group into the ortho-position should render anhydride formation easier, if we may judge from the ease with which phthalic acid forms an anhydride. We know, however, that this is not the case, but that a carboxyl group in the ortho-position usually depresses the rate of ester formation. This objection may be evaded by postulating that the anhydride, once formed, is preserved from attack by the ortho-substituents; but this again implies the introduction of steric considerations. No conclusion can be arrived at on the question until much more material has been collected. Kahn [1] has studied the matter as far as it concerns 3-nitrophthalic acid; but as this seems to be an exceptional substance, not much can be deduced from his results.

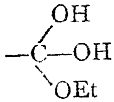
A fourth explanation, which seems the most satisfactory of all, is based upon the assumption that the process of esterification takes place in two phases, during the first of which an unstable intermediate product is formed, whose decomposition constitutes the second phase:—

$$\text{Stage I.}\quad \mathrm{R.C}\begin{matrix}\diagup\mathrm{OH}\\ :\mathrm{O}\end{matrix} \quad + \quad \mathrm{Et.OH} \quad = \quad \mathrm{R.C}\begin{matrix}\diagup\mathrm{OH}\\ -\mathrm{OH}\\ \diagdown\mathrm{OEt}\end{matrix}$$

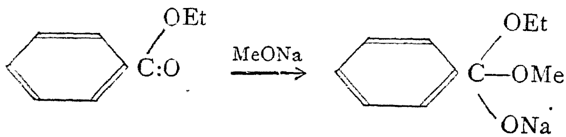
$$\text{Stage II.}\quad \mathrm{R.C}\begin{matrix}\diagup\mathrm{OH}\\ -\mathrm{OH}\\ \diagdown\mathrm{OEt}\end{matrix} \quad = \quad \mathrm{R.C}\begin{matrix}:\mathrm{O}\\ \diagdown\mathrm{OEt}\end{matrix} \quad + \quad \mathrm{H_2O}$$

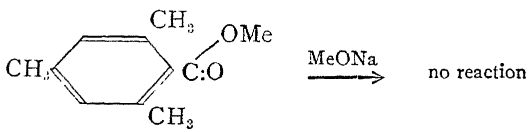
[1] Kahn, *Ber.*, **35**, 3431 (1902).

Obviously, the intermediate compound contains a bulky group:—



and such a compound can only be formed if there be sufficient free space in the molecule to allow of the entrance of a molecule of alcohol. If we reduce the free space by the introduction of substituent groups, we shall diminish the possibility of the intermediate compound being formed, and thus, indirectly, the possibility of ester formation. This hypothesis has been put forward at different times by Henry,[1] Wegscheider,[2] and Angeli.[3] It has received experimental confirmation to some extent from the work of H. v. Pechmann,[4] who found that when benzoic ester was treated with sodium methylate, it yielded a solid product, (I.), while mesitylene carboxylic methyl ester was unattacked, (II.). The difference between the two compounds may be ascribed to the fact that in (II.) the space necessary for the formation of the addition product is occupied by the two methyl radicals:—

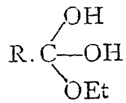
(I.) 

(II.) 

Even if we disregard the steric view, this hypothesis

[1] Henry, *Ber.*, **10**, 2041 (1877)
[2] Wegscheider, *Monatsh.*, **16**, 137 (1895).
[3] Angeli, *Atti. R. Accad. Lincei*, [5] I., 84 (1896)
[4] von Pechmann, *Ber.*, **31**, 503 (1898)

appears to be the best one. For example, the esterification phenomena are explained on the hypothesis of the nascent carbonyl group[1] by the formation of the same addition product



but space influences are not utilised, the following conception being employed instead. The amount of ester formed depends upon the amount of intermediate compound formed: this is self-evident, for if no intermediate compound at all were produced, there could be no ester formation. Further, the amount of intermediate product produced depends upon the reactivity of the carbonyl radical of the carboxyl group, for it is here that the addition takes place. The influences which affect ester formation are therefore those which affect the reactivity of this carbonyl radical; and, as Stewart and Baly have shown, there is no necessity to assume that steric influences have any great effect on the process.

In closing this section, we may give a few instances of the manner in which the Esterification Law can be applied to practical problems.

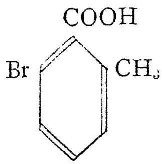
The chief application is to be found in the determination of the constitutions of acids which are otherwise uncertain. We have pointed out early in this section that, in the case of an unsymmetrical succinic acid, the two carboxyl groups show different capabilities of ester formation: a tertiary group being much less easy to esterify than a primary one. By applying Blaise's method[2] it is easy to show whether a given succinic acid is symmetrically substituted or not, for in the former case the fraction :—

$$\frac{\text{Amount of acid ester formed}}{\text{Amount of neutral ester formed}}$$

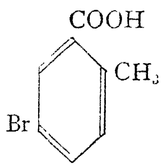
[1] Stewart and Baly, *Trans.*, **89**, 489 (1905).
[2] Blaise, *Compt. rend.*, **126**, 753 (1898).

would be less than unity, while in the case of the unsymmetrically substituted acid it would be greater than unity.

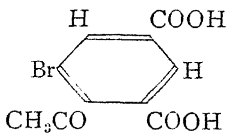
Racine[1] prepared a bromo-toluylic acid to which he ascribed the formula :—



Victor Meyer,[2] from an examination of its rate of esterification, was able to assign to it the correct formula :—

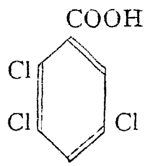
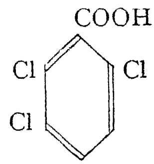


Zincke and Francke[3] found that a certain aceto-bromo-isophthalic acid gave a practically quantitative yield of ester; and from the Esterification Law they concluded that it must be :—



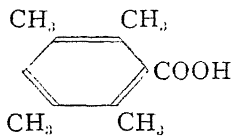
Matthews[4] synthesised a new trichlorobenzoic acid. At that time the only two trichlorobenzoic acids left unidentified were those of the formulae (I.) and (II.) :—

[1] Racine, *Annalen*, **239**, 75 (1885).
[2] V. Meyer, *Ber.*, **28**, 187 (1895).
[3] Zincke and Francke, *Annalen*, **293**, 123 (1896).
[4] Matthews, *Proc.*, **16**, 187 (1900).

(I.)   (II.)

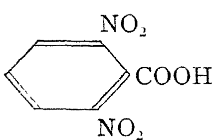
Since Matthews' acid was easily esterified, he decided that it must have the constitution (I.).

Victor Meyer also applied the Esterification Law to the correction of erroneous data. For example, Claus[1] stated that 2,3,5,6-tetramethyl benzoic acid :—



was easily esterified; but Victor Meyer[2] showed that it gave only one per cent. of ester by the usual method; and from this he deduced that Claus had probably been dealing not with durol carboxylic acid, but with some unknown isomer.

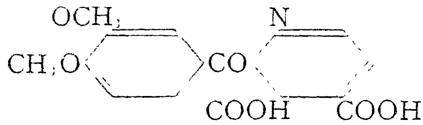
Another application of the Esterification Law is to be found in the case of the separation of two isomeric substances from one another. Martz[3] found that on nitrating *o*-nitrobenzoic acid, all the three possible dinitrobenzoic acids were formed, and that the diorthodinitrobenzoic acid :—



could be separated from the others by utilising the fact that it is much more difficult to esterify than the two isomeric acids

[1] Claus, *Ber.*, **20**, 3101 (1887).
[2] V. Meyer, *Ibid.*, **29**, 831 (1896).
[3] See V. Meyer and Sudborough, *Ibid.*, **27**, 3147 (1894).

are. It is not always safe to lay too much stress upon determinations of constitution by such means, however, unless they are supported by other evidence; for Wegscheider[1] has observed that papaverinic acid:—



Papaverinic acid.

yields a considerable quantity of neutral ester, which was not to be expected if the Esterification Law held good rigidly.

It may be pointed out that the esterification method employed by Marckwald and McKenzie[2] for the resolution of racemic compounds depends upon a modification of the esterification law.

§ III.—*HYDROLYSIS.*

The process of hydrolysis may be expressed in general terms by the equation:—

$$R.CO.X + H_2O = R.CO.OH + X.H$$

In the light of the facts which will be dealt with in the following section, it seems probable that the process, like that of esterification, takes place in two stages, one of addition, the other of decomposition, as follows:—

$$\text{Stage I.}\quad R.CO.X \quad + \quad H_2O \quad = \quad R.C{\begin{array}{l} \diagup OH \\ -X \\ \diagdown OH \end{array}}$$

$$\text{Stage II.}\quad R.C{\begin{array}{l} \diagup OH \\ -X \\ \diagdown OH \end{array}} \quad = \quad R.CO.OH \quad + \quad X.H$$

[1] Wegscheider, *Monatsh.*, **23**, 369 (1902).
[2] Marckwald and McKenzie, *Ber.*, **34**, 469 (1901).

It is obvious that the formation of the large group in the intermediate compound can only occur if there be a certain amount of free space around the carbonyl radical, and in those cases where such space is not found, the hydrolysis will not be possible. Now, it has been observed that in certain cases hydrolysis does not occur, and that in others it takes place only to a limited extent; but in all such cases the number and positions of the groups of atoms in the vicinity of the carbonyl group tend to support the idea that in these instances a lack of free space around the carbonyl group is the cause of the hindrance.

In 1885, Reicher[1] investigated the rate of hydrolysis of certain esters, and was able to prove that the velocity of esterification depended partly upon the nature of the acid radical, and partly upon that of the alcoholic radical. For example, using the acetates of various alcohols he found the following hydrolysis constants :—

		Hydrolysis constant.
$CH_3.OH$	Methyl alcohol	3·493
$CH_3.CH_2.OH$	Ethyl alcohol	2·307
$CH_3.CH_2.CH_2.OH$	Propyl alcohol	1·920
$(CH_3)_2.CH.CH_2OH$	Isobutyl alcohol	1·618
$(CH_3)_2.CH.CH_2.CH_2.OH$	Iso-amyl alcohol	1·645

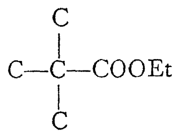
The difference between isobutyl and iso-amyl alcohol indicates that the accumulation of substituents near the hydroxyl group has a hindering effect upon the reaction. The same influence is noticeable in the case of the acids, as is shown by the hydrolysis constants of the ethyl esters of the following acids :—

		Hydrolysis constant.	Affinity constant.
CH_3COOH	Acetic acid	3·204	0·0018
CH_3CH_2COOH	Propionic acid	2·816	0·0013
$CH_3CH_2CH_2COOH$	Butyric acid	1·702	0·0015
$(CH_3)_2.CH.COOH$	Isobutyric acid	1.731	0·0014
$(CH_3)_2.CH.CH_2.COOH$	Isovaleric acid	0·641	0·0017

[1] Reicher, *Annalen*, **228**, 257 (1885); **232**, 103 (1886); **238**, 276 (1887).

From a comparison between the hydrolysis constants and the affinity constants of the various acids, it can be seen that the affinity constant cannot be the preponderating factor in this reaction.

Hjelt[1] showed that in the case of the alkyl-malonic acids the ethyl-, propyl-, iso-butyl-, and allyl-derivatives can be hydrolysed almost as easily as malonic ester itself; while isopropyl- and benzyl-malonic esters are much more difficult; and the reaction goes very slowly indeed in the case of the dialkylated esters. Diallyl-malonic acid has an affinity constant nine times as great as malonic acid, yet its ester is five times as difficult to saponify. Hjelt adopted Bischoff's dynamic hypothesis to explain the results of his investigations. In some further researches on the tribasic acids[2] he found that the group :—



produced effects similar to that found in the malonic series.

Sudborough and Feilmann[3] carried out a series of investigations on the hydrolysis of esters, and came to the conclusion that two factors were concerned in the reaction: (1) the configuration of the acid, or, in other words, the presence of substituted groups situated close to the carboxyl group; and (2) the strength of the acid, determined by its affinity constant. In most cases the first factor is the more prominent, and obscures to a large extent the influence of the second; but when the strength of an acid has been greatly increased by the chemical action of substituents, the second factor becomes more prominent, and conceals the influence of the configuration.

Bischoff and Hedenstrom[4] have studied the hydrolysis of

[1] Hjelt, *Ber.*, **29**, 110 (1896).

[2] Hjelt, *ibid.*, **29**, 1867 (1896).

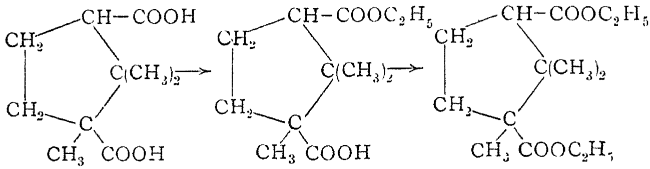
[3] Sudborough and Feilmann, *Proc.*, **13**, 241 (1897).

[4] Bischoff and von Hedenstrom, *Ber.*, **35**, 4094 (1902).

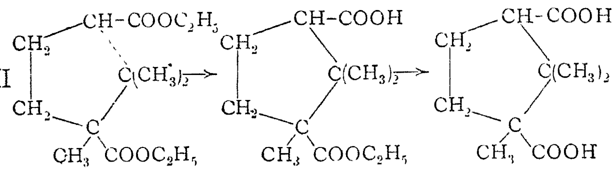
aryl- and benzyl-esters of dibasic acids. Their conclusions are in general the same as those given above, though many irregularities were found in the course of the work.

In the section upon esterification it was pointed out that when camphoric acid was esterified by means of alcohol and hydrochloric acid the secondary carboxyl group was esterified before the tertiary one, (I.). The same is found to be the case when the di-ester is hydrolysed, for in this case the tertiary carboxyl is harder to free from its ethyl group, (II.). Similar results are found with homocamphoric acid :—

I



II



Anschutz[1] observed a similar case in the unsaturated acids, for when mesaconic acid is esterified it yields the ester (I), while if the di-ester be partially hydrolysed, the product is the isomeric mono-ester (II.) :—

(I.) $CH_3.C.COOH$ ‖ $H.C.COOR$ $\qquad$ $CH_3.C.COOR$ ‖ $H.C.COOH$ (II.)

In the case of the hydrolysis of aromatic esters, the most complete data are to be found in papers by Victor Meyer and

[1] Anschutz, *Ber.*, **30**, 2652 (1897).

Kellas,[1] the principal results of which are given in the table below :—

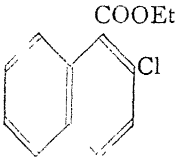
	I	II.	III.	IV.	V.
Benzoic acid . .	74·20	22·35	13·95	17·47	—
o-Toluic acid .	13·82	1·98	—	2·44	5·74
m- ,, ,, . .	—	—	—	—	6·46
p- ,, ,, . .	—	8·28	—	—	6·22
o-Chlorobenzoic acid	88·39	—	15·70	13·69	—
m- ,, ,, .	—	—	27·56	—	—
p- ,, ,, .	—	25·84	16·56	—	—
o-Bromobenzoic acid	—	—	—	10·58	—
m- ,, ,, .	—	—	24·45	—	—
p- ,, ,, .	—	26·14	16·80	—	—
o-Iodobenzoic acid	64·24	—	—	7·23	—
m- ,, ,, .	—	—	—	—	—
p- ,, ,, .	—	26·37	—	—	—
o-Nitrobenzoic acid	96·62	44·43	—	29·9	—
m- ,, ,, .	94·84	85·17	—	—	—
p- ,, ,, .	94·45	90·97	—	—	—

Of the above figures, which represent the amounts of ester hydrolysed, those in each of the vertical columns I., II., III., IV., and V. were obtained under the same conditions, and are therefore comparable with one another. From the table it will be seen that a methyl group in the meta- or para-position hinders the reaction, while chlorine, bromine, iodine, and the nitro-group accelerate it. The methyl group exerts most effect in the ortho-position, as was to be expected, if the influence were stereochemical.

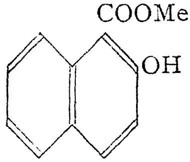
In the naphthalene series the carbon atoms of the second benzene ring can play the part of an ortho-substituent in the case of α-carboxylic acids. This is shown by the following results of Victor Meyer[2] :—

[1] V. Meyer and Kellas, *Ber.*, **28**, 1258 (1895) ; *Zeit. physikal. Chem.*, **24**, 243 (1897).

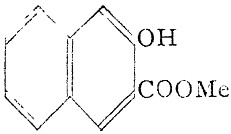
[2] V. Meyer, *Ber.*, **28**, 1262 (1895).



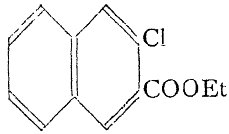
(I.)



(II.)



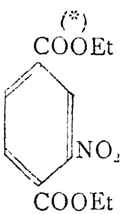
(III.)

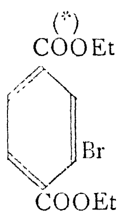


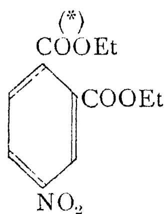
(IV.)

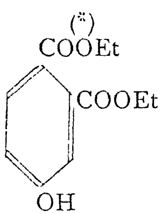
Under like conditions, compounds (I.) and (II.) gave very small quantities of acid, while (III.) was hydrolysed to the extent of 30 per cent., and (IV.) to 71 per cent.

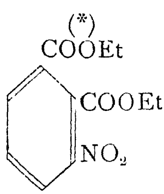
Even a second carboxyl group may exercise a hindering influence upon the hydrolysis of an ester. The following formulæ[1] show the results of hydrolysing one group in a dicarboxylic acid, the one marked with an asterisk being that which hydrolyses first :—



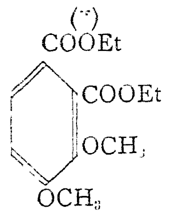


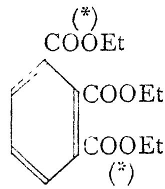






[1] Wegscheider and others, *Monatsh.*, **16**, 75 (1895) ; **21**, 787 (1900) ;





C. A. Bischoff and A. von Hedenstrom[1] have made an exhaustive examination of the velocities of hydrolysis in the cases of aryl- and benzyl-esters of dibasic acids. Their tables of results cannot be reprinted here, but should be consulted in the original paper.

On treatment with water, acid chlorides are converted into the corresponding acid, hydrochloric acid being eliminated :—

$$R.CO.Cl + H_2O = R.CO.OH + HCl$$

But in the case of certain aromatic acids, this reaction may be hindered or even prevented by the presence of ortho-substituents in the molecule. The first observation on the point was made by Victor Meyer,[2] who found that 2,4,6-trinitro-benzoyl chloride was hardly changed even after being boiled with water for an hour; the chloride of 2,4,6-trichloro-benzoic acid is even more stable. Sudborough[3] investigated the question thoroughly, using the following compounds: *o*-, *m*-, and *p*-bromobenzoyl chloride; 2,4-, 3,5-, and 2-6-dibromo-benzoylchloride; 3,4,5-, and 2,4,6-tribromobenzoyl chloride; 2,3,4,6-tetrabromobenzoyl chloride. His experiments showed (1) that acid chlorides which do not contain bromine atoms in the ortho-positions are readily decomposed by sodium hydrate solution (20 c c. of an 8 per cent. solution to 0·5 grammes of the acid chloride) in most cases before the solution begins to boil; in no case does the decomposition

23, 359, 393 (1902); McKenzie, *Trans.*, **79**, 1135 (1901); Graebe and Leonhardt, *Annalen*, **290**, 225 (1896).

[1] Bischoff and von Hedenstrom, *Ber.*, **35**, 4094 (1902).

[2] V. Meyer, *ibid.*, **27**, 3153 (1894).

[3] Sudborough, *Trans.*, **65**, 1028 (1894); **67**, 587 (1895).

require more than ten seconds' boiling; (2) that those acid chlorides which are substituted by one bromine atom in the ortho-position are somewhat more stable, and are only completely decomposed after boiling for two to three minutes with alkali; (3) acid chlorides having two bromine atoms in the ortho-position are extremely stable. Lütjens[1] found that the dichloride of tetra-iodo-terephthalic acid was so stable that it was almost unaffected by heating with water for several hours at 150° C. It is probable that the conversion of the acid chloride into the acid takes place through an intermediate product as shown in the scheme below; and that in the case of ortho-substituted acid chlorides there is not sufficient space available to allow the formation of the intermediate substance.

$$\mathrm{R.C}\begin{array}{l}\nearrow\!\!\!\!\nearrow \mathrm{O} \\ \searrow \mathrm{Cl}\end{array} + \mathrm{H_2O} = \mathrm{R.C}\begin{array}{l}\nearrow \mathrm{OH} \\ -\mathrm{OH} \\ \searrow \mathrm{Cl}\end{array} = \mathrm{R{-}C}\begin{array}{l}\nearrow \mathrm{OH} \\ = \mathrm{O}\end{array} + \mathrm{HCl}$$

Under certain conditions, nitriles have the faculty of adding on first one molecule of water and then a second :—

$$\begin{aligned} &\mathrm{R.C{:}N} + \mathrm{H_2O} = \mathrm{R.CO.NH_2} \\ &\mathrm{R.CO.NH_2} + \mathrm{H_2O} = \mathrm{R.CO.ONH_4} \end{aligned}$$

Merz and Weith[2] were the first to notice abnormalities in the behaviour of certain nitriles: they found that the ordinary methods did not suffice to convert perchlorbenzonitrile, hexa-chlor-α-naphthonitrile, or perbrombenzonitrile into the corresponding acid. Even after being heated to 200° C. with a solution of hydrochloric acid in glacial acetic for twenty hours these nitriles were not hydrolysed. Hofmann[3] observed a similar phenomenon in the cases of 2,3,4,6-tetramethyl-benzo-nitrile and pentamethyl-benzonitrile.

Jacobson[4] having by another method obtained the amide

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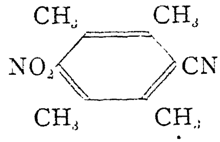
[1] Lutjens, *Ber.*, **29**, 2823 (1896).
[2] Merz and Weith, *ibid.*, **16**, 2886 (1883).
[3] Hofmann, *ibid.*, **17**, 1915 (1884).
[4] Jacobson, *ibid.*, **22**, 1219 (1889).

corresponding to pentamethyl-benzonitrile, showed that it could not be converted into pentamethyl-benzoic acid by the usual reactions.

Cain[1] found that nitrodurolic nitrile was not easily hydrolysed :—



It will be noticed that in all these cases the nitrile group has on either side of it an ortho-substituent. From later researches, especially those of Claus,[2] it appears that one substituent in the ortho-position suffices to bring about a considerable hindrance to the hydrolysis of a nitrile; while two ortho-substituents increase the difficulty still further. From this it has been deduced that the obstruction is due to the space relations of the groups. It is evident that when a nitrile group is transformed into an amido group and this in turn into a carboxyl radical, a more bulky group is being formed in each case. Now, the space around the nitrile radical is limited by the presence of the two groups in the ortho-position, which take up a certain amount of room, and in some cases it must be supposed that there is not sufficient space available to allow of the extra atoms entering the molecule.

The same phenomena are found in some cases in the fatty series. For instance, Pschorr and Wolfes[3] noticed that acid hydrolysing agents had no effect upon α-phenyl-*o*-nitrocinnamic nitrile, (I.), α-*p*-nitrophenyl-*o*-nitrocinnamic nitrile, (II.), or α-*p*-methoxyphenyl-*o*-nitrocinnamic nitrile, (III.):—

$$\begin{array}{rl} & \text{(I.)} \\ (o)\ & NO_2.C_6H_4\text{—}C\text{—}H \\ & \qquad\qquad\ \ \| \\ & \qquad C_6H_5\text{—}C\text{—}CN \end{array} \qquad \begin{array}{rl} & \text{(II.)} \\ (o)\ & NO_2.C_6H_4\text{—}C\text{—}H \\ & \qquad\qquad\ \ \| \\ (p)\ & NO_2.C_6H_4\text{—}C\text{—}CN \end{array}$$

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[1] Cain, *Ber.*, **38**, 969 (1895).
[2] Claus, *Annalen*, **265**, 364 (1891).
[3] Pschorr and Wolfes, *Ber*, **32**, 3399 (1899).

(III.)

$$\begin{array}{l} (o)\ NO_2.C_6H_4{-}C{-}H \\ \qquad\qquad\qquad\quad \| \\ (p)\ CH_3O.C_6H_4{-}C{-}CN \end{array}$$

while alcoholic reagents also produced no hydrolysis, but instead gave rise to considerable changes in the constitutions of the substances.

As mentioned above, amides have the property of adding on one molecule of water to form the ammonium salts of acids. This reaction, being the second half of the hydrolysis of nitriles, is liable to the same hindrances as were noted in that case. The subject has been studied by Claus[1] as well as by Sudborough[2] and others. The results are similar to those found in the case of the nitriles. Remsen and Reid[3] have estimated the constants of hydrolysis for some substituted amides, and found the following results: benzamide has a coefficient of 0·0209.

Name.	Ortho-	Meta-	Para-
Tolamide	0·00220	0·0193	0·0175
Amidobenzamide	0·00178	0·0177	0·0198
Hydroxybenzamide	0·00437	—	—
Methoxybenzamide	0·0116	—	—
Ethoxybenzamide	0·0093	—	—
Chlorobenzamide	0·00321	—	0·0179
Bromobenzamide	—	0·0184	0·0146
Iodobenzamide	0·00106	—	—
Nitrobenzamide	0·00054	0·0196	0·0236

Observations of this class may serve to decide questions as to the constitution of certain amides. For instance,

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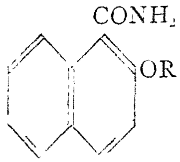
[1] Claus, *J. pr. Chem.*, **37**, 197 (1888); *Annalen*, **265**, 364 (1891); **266**, 223 (1891); **269**, 208 (1892).

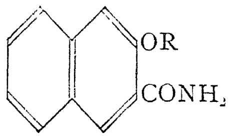
[2] Sudborough, *Trans.*, **67**, 601 (1895); Sudborough, Jackson, and Lloyd, *ibid.*, **71**, 229 (1897).

[3] Remsen and Reid, *Amer. Chem. J.*, **21**, 340 (1899).

Gattermann[1] synthesised an amide which had one of the following formulæ :—



(I.)



(II.)

As the actual compound could not be hydrolysed, there seemed no reason to doubt that it had the formula (I.), as there is no second ortho-substituent in (II.). It should be noted that the second benzene ring here plays the same part as a group in the ortho-position might be expected to do.

Remsen and Reid[2] found that in the case of some sulphonamides the same relations between substitution and hydrolysis held good: *o*-sulphamido-benzoic acid cannot be hydrolysed by boiling with dilute sulphuric acid, while the para-isomer yields easily to this treatment.

A further step was made by Fischer's discovery[3] that substitution in the α-position has analogous effects in the fatty series. For instance, the amounts of amide hydrolysed in equal times are shown for several acids in the malonic series by the figures below :—

Malonamide	89 per cent.
Monopropyl-malonamide . .	57 ,,
Diethyl-malonamide . . .	3 ,,

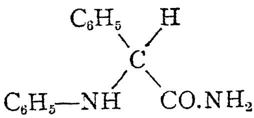
But, on the other hand, in half the time no less than fifty-six per cent. of dimethyl-malonamide was hydrolysed.

Sachs and Goldmann[4] found that while the amides (I.) and (II.) could be easily hydrolysed, (III.) is rather difficult, and, in

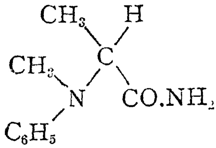
[1] Gattermann, *Annalen*, **244**, 75 (1888).
[2] Remsen and Reid, *Amer. Chem. J.*, **21**, 281 (1899).
[3] Fischer, *Ber.*, **35**, 852 (1902).
[4] Sachs and Goldmann, *ibid.*, **35**, 3325 (1902).

the case of (IV.), hydrolysis could not be brought about at all:—

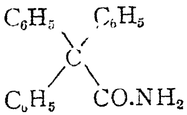
(I.)



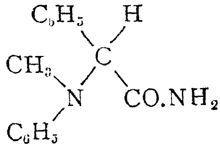
(II.)



(III.)



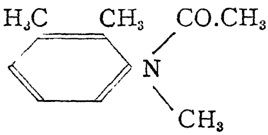
(IV.)



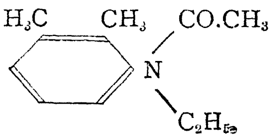
Here evidently the replacement of a hydrogen atom by a methyl group, or of a methyl by a phenyl radical brings about a lessening of the available space round the amido group.

Aromatic substituted amides of the type Ar-NR.CO.R can usually be broken down by hydrolysing agents into their parent acid and base; but certain observations of Menton[1] have shown that this reaction may be hindered by the presence of ortho-substituents in the benzene nucleus. He found that neither acetyl-methyl-orthoxylidine, (I.), nor acetyl-ethyl-orthoxylidine, (II.) can be easily broken down. If we consider the formulæ of these substances it seems probable that space relations play some part in the reaction, though it is not at present possible to define their action.

(I.)

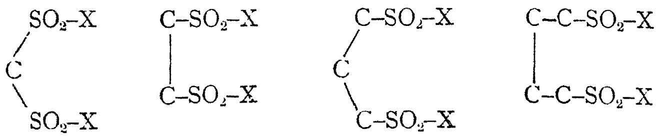


(II.)



[1] Menton, *Annalen*, **263**, 317 (1891).

Autenrieth and Hennings [1] have investigated the hydrolysis of disulphones, and find that α-, γ-, and δ-disulphones are not hydrolysable either when the two sulpho-groups belong to an open chain or when they are attached to a ring. The β-disulphones alone are capable of being hydrolysed. When the formulæ of all these compounds are compared, it is apparent that in the case of the β-compounds the groups X. are in the "critical position" 1:6 to one another, and thus the case appears to agree with Bischoff's Dynamic Hypothesis.



(α) (β) (γ) (δ)

§ IV. *CHAIN FORMATION.*

The question of the influence of the space arrangements of atoms upon chain formation has been most carefully examined, Bischoff alone having published nearly seventy papers on the subject. In the present section a summary will be given of the more important parts of his investigations; and the researches of other workers will also be described.

It is obviously impossible to analyse all of Bischoff's *Studies in Chain Formation*,[2] but as he has summarised most of his results in four papers [3] (Nos. VI., XXXII., XLI., and

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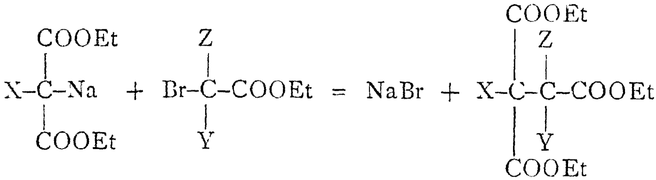
[1] Autenrieth and Hennings, *Ber.*, **35**, 1388 (1902).

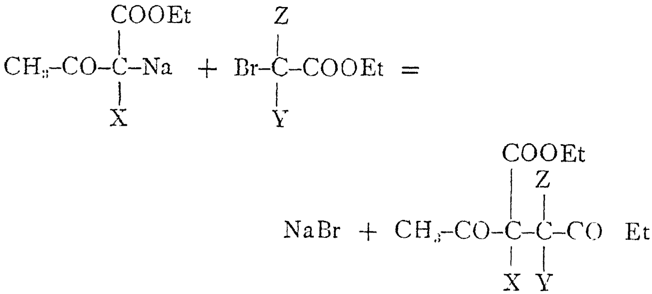
[2] *Ber.*, **28**, 2616, 2824 (1895); **29**, 966, 972, 979, 982, 1276, 1280, 1286 1504, 1514, 1741 (1896); **30**, 487, 2303, 2310, 2315, 2464, 2469, 2476, 2760, 2764, 2769, 2976, 3169, 3174, 3178 (1897); **31**, 2672, 2678, 2839, 2847, 3015, 3025, 3236, 3241, 3248 (1898); **32**, 1748, 1755, 1761, 1940, 1948, 1953 (1899); **33**, 924, 931, 1249, 1261, 1269, 1386, 1392, 1398, 1591, 1603, 1668, 1676, 1686 (1900); **34**, 1835, 1844, 2057, 2125, 2135 (1901); **37**, 4341, 4350, 4356, 4548, 4556, 4653 (1904); **39**, 3830, 3840, 3846, 3854 (1906).

[3] *Ibid.*, **29**, 982 (1896); **31**, 3025 (1898); **32**, 1953 (1899); **33**, 1603 (1900).

LI.), we may deal with these, including in our survey, when necessary, results from other papers.

In his first researches, Bischoff dealt with the alkylation of malonic and acetoacetic esters by allowing their sodium derivatives to react with bromine derivatives of various alkyl radicals. As an example of his work we may describe the case of the action of α-bromo fatty esters upon the sodium derivatives of malonic and acetoacetic ester. The reactions normally follow the courses shown in the equations :—



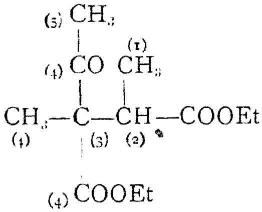


In addition to using the parent substances, Bischoff employed the methyl, ethyl, propyl, iso-propyl, iso-butyl, iso-amyl and allyl derivatives of malonic and acetoacetic esters; and with these he combined the α-bromo-derivatives of propionic, butyric, iso-butyric and iso-valerianic esters. His conclusions may be summarised as follows :—

I. On the whole, it was found that when any given bromo-fatty ester was combined with a certain derivative of aceto-acetic ester the yield obtained was not so good as was produced from the corresponding malonic ester derivative; *e.g.* if α-bromo-propionic acid were combined with the sodium derivative of methyl-acetoacetic ester and with methyl-malonic

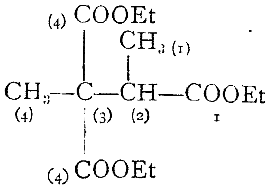
ester, a greater proportion of the normal product would be formed in the latter case than in the former. Bischoff explains this by means of his Dynamic Hypothesis in the following way. The two reaction products in the example given will be :—

(I.)



Acetoacetic ester product.

(II.)

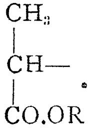


Malonic ester product.

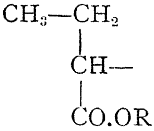
An inspection of them shows that while each of them has three carbon atoms in the 1,4-position to the carboxylic ester group at the end of the chain, (I.), which is the product of the acetoacetic ester synthesis, has in addition another carbon atom in the 1,5-position, which is the critical position on Bischoff's hypothesis. This extra carbon atom appears to be sufficient to turn the scale in favour of the malonic ester synthesis.

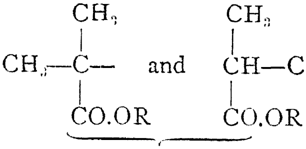
II. As regards ease of chain formation, Bischoff finds that the fatty acid radicals are grouped in the following order, those which react most easily being placed first :—

(I.)

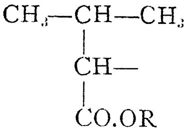


(II.)



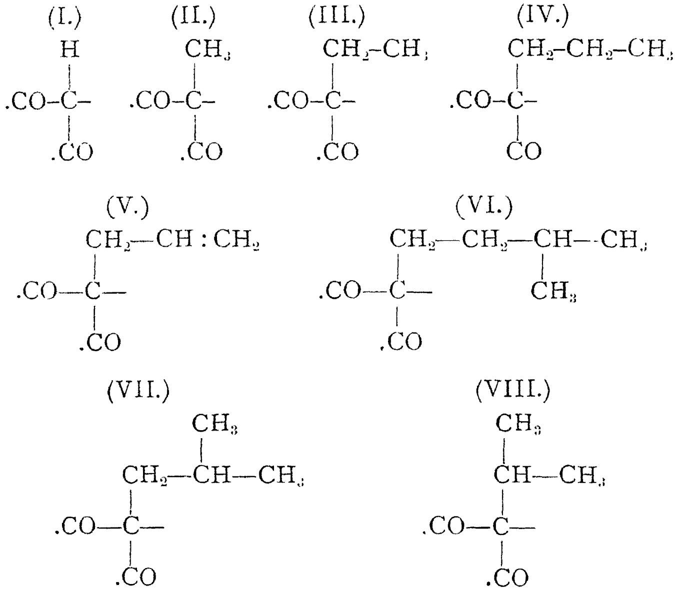


(III.)



(IV.)

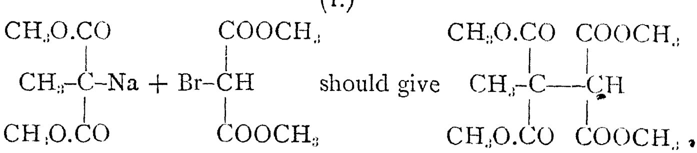
III. The malonic ester radicals react in the following order of ease, the most reactive being placed first :—



IV. It appears that in the case of acetoacetic ester, the limit of the chain formation is reached with the ethyl derivative, as even bromo-propionic ester does not react with this to any extent.

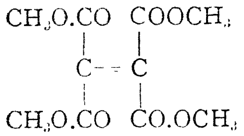
In his next series of researches, Bischoff studied the effect of treating a mixture of malonic ester and bromo-malonic ester with sodium ethylate, in the hope of coupling together two molecules of the ester :—

(I.)

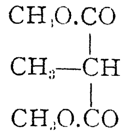


und, however, that instead of the reaction following this ;, half of the compound reacted in this way and half in er, so that the other two products were :—

(II.)

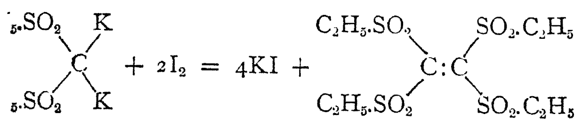


(III.)

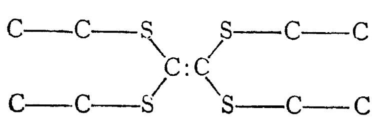


is evident that during the course of the second reaction imber of substituents in the 1,4-position has not been at as it would have been, had the whole compound been formula (I.). This does not illustrate the Dynamic hesis, but it is a good example of the effect of space ices upon the course of reactions.

the thirteenth of his *Studies*, Bischoff showed that the ice of elements other than carbon in the chain did not his results to any great extent. The reaction which he was that between the di-potassium derivative of methyiethyl-sulphone and iodine. The normal reaction would ected to take the form :—



vould bring each sulphur atom into the 1,5-position to carbon atoms, *i.e.* twelve 1,5-positions in all; and it also bring four carbon atoms each into the 1,6-position espect to other three, *i.e.* twelve 1,6-positions in all, as seen in the skeleton formula below :—



n accumulation of substituents in these critical positions

would be most unlikely if the Dynamic Hypothesis held good; and, in point of fact, it was shown that instead of this compound being formed, the reaction took quite a different course, leading to a compound in which there is no possibility of collisions between groups in the 1,5 and 1,6-positions. The sulphone potassium derivative reacts with iodine thus:—

$$\begin{array}{l} C_2H_5.SO_2\diagdown \\ \qquad\qquad CK_2 \\ C_2H_5.SO_2\diagup \end{array} + 4I_2 = 2KI + \begin{array}{l} C_2H_5.SO_2\diagdown \\ \qquad\qquad CI_2 \\ C_2H_5.SO_2\diagup \end{array}$$

and in the reaction product the number of atoms in the 1,5- and 1,6-positions to each other is no greater than in the original compound. It appears from this that Bischoff's hypothesis may be applied to some cases in which the chain is not wholly composed of carbon atoms. This was confirmed by allowing the sodium derivative of malonic ester to react with the di-iodo-derivative of methylene diethyl-sulphone. Instead of taking the first course, which would have involved the formation of many 1,5- and 1,6-substituents, the reaction followed the lines of the second equation:—

(I)

$$2(EtO.CO)_2CHNa + (Et.SO_2)_2CI_2 =$$

$$2\ NaI + \begin{array}{ccc} (EtO.CO)_2CH & & (SO_2.Et) \\ & \diagdown\ \diagup & \\ & C & \\ & \diagup\ \diagdown & \\ (EtO.CO)_2CH & & (SO_2.Et) \end{array}$$

(II.)

$$2(EtO.OC)_2CHNa + (Et.SO_2)_2CI_2 =$$

$$2NaI + (EtO.OC)_2C : C(COOEt)_2 + CH_2(SO_2.Et)_2$$

In his next series of papers, Bischoff investigated the course of the reactions between esters of α-bromo-fatty acids and certain aromatic bases; that is to say, the general reaction:—

$$2\begin{array}{c} X \\ | \\ NH \\ | \\ Y \end{array} + Br-\begin{array}{c} a \\ | \\ C \\ | \\ b \end{array}-COOEt = \begin{array}{c} X \\ | \\ NH.HBr \\ | \\ Y \end{array} + \begin{array}{c} X \\ | \\ N \\ | \\ Y \end{array}-\begin{array}{c} a \\ | \\ C \\ | \\ b \end{array}-COOEt$$

It was found that the experimental errors amounted to about five per cent., so that any differences less than this cannot be considered important. The following table summarises the results obtained :—

			$a = CH_3$, $b = H$		$a = C_2H_5$, $b = H$	
X	Y		100° Per cent.	120–130° Per cent.	100° Per cent.	120–130° Per cent.
$C_6H_5.CH_2$	H	Benzylamine	98	—	—	94
C_6H_5	H	Aniline *	95	95	—	86
$CH_3.C_6H_4$	H	*m*-Toluidine	94	—	—	87
$CH_3.C_6H_4$	H	*p*-Toluidine	92	93	—	93
$(CH_3)_2.C_6H_3$	H	*m*-Xylidine	91	96	—	89
$(CH_2)_5.N$	H	Piperidine	91	—	88	—
$Cl.C_6H_4$	H	*p*-Chloraniline	92	—	—	—
C_6H_5	C_2H_5	Ethylaniline	79	96	22	66
$CH_3.C_6H_4$	H	*o*-Toluidine *	80	96	—	81
$NO_2.C_6H_3.CH_3$	C_2H_5	1,2,4 Nitro-toluidine	71	88	—	—
$Cl.C_6H_4$	H	*o*-Chloraniline	61	—	—	—
$NO_2.C_6H_4$	H	*m*-Nitraniline	59	87	—	—
$NO_2.C_6H_4$	H	*p*-Nitraniline	5	80	—	—
C_6H_5	$CH_2.C_6H_5$	Benzylaniline	0	50	—	13
$NO_2.C_6H_3.CH_3$	H	1,2,5 Nitro-toluidine	0	42	—	—
$NO_2.C_6H_4$	H	*o*-nitraniline	0	14	—	—
$NO_2.C_6H_3.CH_3$	H	1,3,4 Nitro-toluidine	0	7	—	—
C_6H_5	C_6H_5	Diphenylamine	0	0	—	—

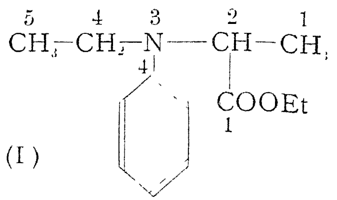
* Cf. with these results papers by H. Goldschmidt and Wachs,[1] and H. Goldschmidt and R. Bräuer.[2]

In many of these cases illustrations of the Dynamic Hypothesis can be found. For instance, if we compare the relative yields of ethyl- or benzyl-aniline with bromo-propionic and bromo-butyric ester, we find the following :—

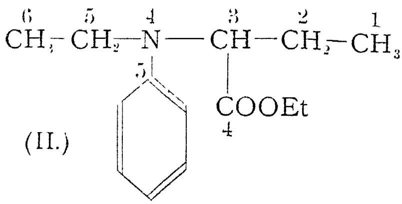
[1] Goldschmidt and Wachs, *Zeit. physikal. Chem.*, **24**, 353 (1897).
[2] Goldschmidt and Bräuer, *Ber.*, **39**, 97 (1906).

I.	Ethylaniline with	propionic ester at 100°	gives	79%
II.	„	„	butyric	„	„	22%
III.	Benzyl-aniline with	propionic ester at 130°	gives	50%
IV.	„	„	butyric	„	„	13%

Now, when we examine the formula of the reaction product in each case, we find that in Case I. we have one carbon atom in the 1,5-position to two others; while in Case II. we have the methyl group (1) in the 1,5-position with respect to the carbon atom (5) and the phenyl group, and also in the 1,6-position to the methyl group (6); further, the methyl group (6) is in the 1,5-position to the groups (2) and (4). Thus, in the formula (II.), we have many more chances of collision between atoms in the critical positions than we have in formula (I.), and the reason for the comparatively small yield of (II.) is apparent.



(I)

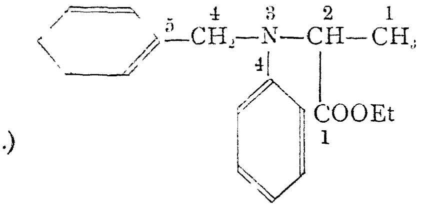


(II.)

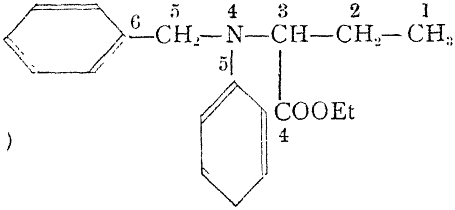
Similar results can be deduced from (III) and (IV.). In (III.) the phenyl group (5) is in the 1,5-position to the groups marked (1); while in (IV.) the phenyl group (6) is in the 1,5-position to the carbon atom (2) and the —COOEt group, and in the 1,6-position to the carbon atom (1); while the phenyl group (5) is in the 1.5-position to (1). Thus here

also the possibilities of collisions are greatly increased by the substitution of butyric for propionic ester in the synthesis.

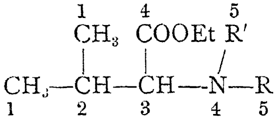
(III.)



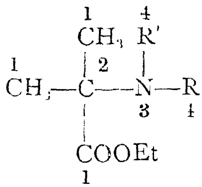
(IV.)



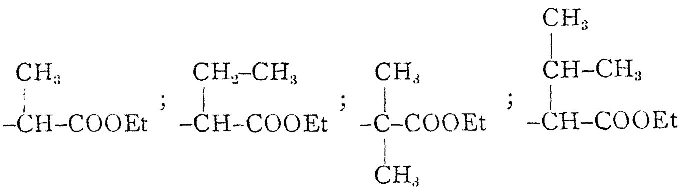
When *a* in the general formula is an iso-propyl group (*i.e.* when α-bromo-isovalerianic ester, $(CH_3)_2CH.CHBr.COOC_2H_5$, is used), an increase in hindrance is found throughout the whole series of reactions. The secondary bases, with the exception of piperidine, hardly react at all. This is probably due to the fact that any group attached to the nitrogen atom in the final product will be in the 1,5-position to the two methyl radicals of the ester.



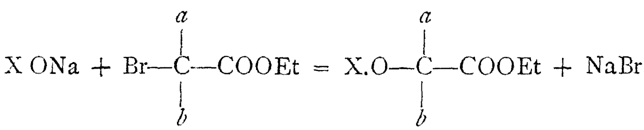
In contrast to this, it is found that when both *a* and *b* are methyl groups (*i.e.* in the case of iso-butyric ester), a distinct improvement in the yields is observed. This is apparently due to the fact that the methyl groups, instead of being in the 1,5-position to radicals attached to the nitrogen atoms, as is the case in the above formula, are now in the 1,4-position, as shown below :—



We have, therefore, the following scale, in which those groups with least hindering effect are placed first :—



The next subject of Bischoff's investigations was the reaction between α-bromo-fatty esters and various sodium alcoholates, the general equation of which is as follows :—



Bischoff anticipated that the yield of alkyloxy-ester would be greatest when the spacial factors in the reaction allowed the closest proximity between the sodium and bromine atoms. Now, if we consider the Dynamic Hypothesis more closely than we have already done, we shall see that it depends, not merely upon the collisions between two atoms A and B, but upon the possibility of the atom A driving the atom B out of a certain sphere, and itself entering this sphere. It is evident that we must go a step further, and try to discover if there are any forces at work which will tend to bring the atom B back into the sphere of action from which it was driven. If we write down the two formulæ :—

$$\text{(I.)} \quad \begin{array}{ccccc} & Z & & B & \\ & | & & | & \\ - & C & - & C & - X \\ & | & & | & \\ & Y & & R & \end{array} \qquad\qquad \begin{array}{ccccc} & & B & & \\ & & | & & \\ H & - & C & - & X \\ & & | & & \\ & & H & & \end{array} \quad \text{(II.)}$$

and suppose that the atom A of which we spoke is approaching X, with which it is capable of reacting, on Bischoff's view, it will tend to collide with the atom B, and, until it has driven B outside a certain sphere, no reaction between A and X will be possible, owing to their not being able to approach within each other's reaction radius. It is obvious that after the first collision, B will be driven back, and in its turn will collide with either Z, C, or R (Formula (I.)). If these groups are sufficiently massive, they will repel it again into its original position; and if it regains this position before A has had time to approach within the reaction radius of X, the whole process may be repeated an indefinite number of times without A ever being able to react with X. On the other hand, if we suppose that instead of massive groups at Z and R we had small or light ones (for example, if we had hydrogen atoms, as in the second formula), it would be much less probable that the collision of B with them would be sufficient to force B back into the position from which it was driven by A; and, to take an extreme case, if there were no groups at all at Z and R, so that B had nothing to collide with after being forced out of its position by A, then it would not return to that sphere so quickly as in the other cases, and probably would return too late to prevent A approaching X closely enough to react with it. It was with the aim of testing the value of this hypothesis that Bischoff undertook the study of the reaction with which we are about to deal. Since oxygen is divalent, it is apparent that there will be more free space around an oxygen atom than around a carbon atom, for in the one case we have only two groups to deal with, while in the case of carbon there are four in the same space. Therefore, if we have two groups attached together in one case by an oxygen, and in another by a carbon atom, the possibility of collisions occurring between the two groups will be less in the first case than in the second.

From the foregoing, we should expect to find that, in

general, chain formation through an oxygen atom would be easier than through a carbon atom; and that less hindrance would be produced by large groups in the former case than in the latter. Bischoff has shown that this is true by the following method. He dissolved the bromo-ester in ligroin, and then suspended the alcoholate in the solution and boiled it for one hour. At the end of this time he found that the sodium was present in four different compounds :—

(A) as sodium bromide, from the chain formation.

(B) as alcoholate which had not been attacked.

(C) as the sodium salt of the bromo-acid whose ester he had used—the result of hydrolysis.

(D) as a salt of the alkyloxy-acid formed by the reaction.

He used the following alcohols :—

I. Methyl CH_3OH

II. Ethyl C_2H_5OH

III. Propyl $CH_3.CH_2.CH_2.OH$

IV. Butyl $CH_3.CH_2.CH_2.CH_2.OH$

V. Octyl $CH_3.CH_2.CH_2.CH_2.CH_2.CH_2\ CH_2\ CH_2.OH$

VI. Isopropyl
$$\begin{array}{l} CH_3\diagdown \\ \qquad CH.OH \\ CH_3\diagup \end{array}$$

VII. Secondary butyl
$$\begin{array}{l} CH_3.CH_2\diagdown \\ \qquad\qquad CH.OH \\ \qquad CH_3\diagup \end{array}$$

VIII. Isocapryl
$$\begin{array}{l} CH_3.CH_2.CH_2.CH_2.CH_2\diagdown \\ \qquad\qquad\qquad\qquad\qquad CH.OH \\ \qquad\qquad\qquad\qquad CH_3\diagup \end{array}$$

IX. Isobutyl
$$\begin{array}{l} CH_3\diagdown \\ \qquad CH-CH_2.OH \\ CH_3\diagup \end{array}$$

X. Isoamyl
$$\begin{array}{l} CH_3\diagdown \\ \qquad CH.CH_2.CH_2.OH \\ CH_3\diagup \end{array}$$

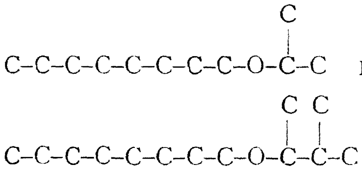
XI. Tertiary butyl
$$\begin{array}{l} \qquad CH_3\diagdown \\ CH_3-C.OH \\ \qquad CH_3\diagup \end{array}$$

The following table gives the results obtained. The letters correspond to those given for the reactions, and the Roman numbers are those of the alcohols in the list above :—

	α-Bromopropionic ester.				α-Bromobutyric ester.			
	A	B	C	D	A	B	C	D
I.	89	0	1	10	84	0	1	15
II.	87	0	0	13	84	1	0	15
III.	84	0	0	16	78	2	2	18
IV.	85·5	1·5	1	12	81	8	3	8
V.	87	2	1	10	—	—	—	—
VI.	77	1	4	18	71	1	3	25
IX.	86	2	2	10	84	2·5	2	11·5
X.	80	1	5	14	79·5	1·5	5	14
XI.	74·5	3	6	16·5	80·5	1	3	15·5
	α-Bromo-isobutyric ester.				α-Bromo-isovalerianic ester.			
I.	84	1	0	15	80	1	1	18
II.	82	1	0	17	74	1	2	23
III.	83	1·5	2	13·5	77	3	3	17
IV.	86	1	2	11	86	8	3	3
V.	75	3·5	1·5	20	67	3	3	27
VI.	76	1	1	22	71	2	4	23
IX.	81	1·5	1	16·5	78	5·5	4	12·5
X.	79·5	1·5	5	14	75	2·5	6	16·5
XI.	78·5	0·5	4·5	16·5	77·5	1·5	5	16

An examination of these figures leads to the following: The effect of a long chain is shown by the difference between the values for octyl alcohol, V., and its predecessor, butyl alcohol, IV. This is not well brought out in the case of A with α-bromopropionic ester, but with α-bromo-isobutyric ester the difference is that between 86 and 75 per cent.; while with α-bromo-isovalerianic ester the difference between the amounts is even greater (86 and 67 per cent.). The hydrolysis constant D is also higher in the case of octyl alcohol than of butyl alcohol, rising from 11 to 20 per cent. with α-bromo-isobutyric ester, and from 3 to 27 per cent. with α-bromo-isovalerianic

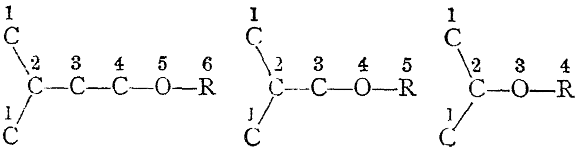
ester. This appears to prove that a long chain can have considerable influence when the other part of the molecule has two forks in it; though, as the figures for α-bromo-propionic ester show, it has little effect when there is only one fork in the second half of the molecule. Schematically, this may be represented thus:—



Favourable.

Unfavourable.

With regard to the alcohols with a single side chain, VI., IX., and X., it appears that they react in the following order, the most reactive being placed first: iso-amyl alcohol, iso-butyl alcohol, and iso-propyl alcohol. As can be seen, this agrees very well with the Dynamic Hypothesis:



X. Iso-amyl. IX. Iso-butyl. VI. Iso-propyl.

since, in the case of X., the carbon atoms (1) have only an oxygen atom in the critical position to them; while in IX. and VI. the critical position lies somewhere in the acid part of the molecule, among carbon atoms.

In his last series of papers, Bischoff studied the reaction between α-bromo-fatty esters and the sodium derivatives of mono- and di-valent phenols. As regards the acids which he used, he was able to prove that the same gradations in reaction velocity were shown in this case as in that of the alcoholates; but as regards the phenols he was unable to arrive at any conclusions on the question of steric hindrance. From his results it appears probable that in this reaction purely chemical influences far outweigh any steric effects.

Bischoff has been by far the greatest worker on the question of chain formation; he appears to have collected almost as much material as the rest of the investigators in this field combined, the only other researches which compare with his in point of completeness being those of Menschutkin,[1] with which we must now deal.

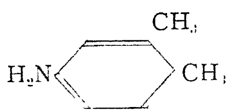
In order to estimate the effect of substitution in the benzene nucleus upon reactions taking place in a side chain, Menschutkin investigated the following reactions, and found the constants given in each case:—

I. Reaction of allyl bromide upon the toluidines—
Meta-, 445. Para-, 96. Ortho-, 54.

II. Reaction of dipropylamine with nitro-bromobenzenes—
Ortho-, 88·8. Para-, 23. Meta-, 0.

III. Reaction of allyl bromide with chloranilines—
Para-, 34. Meta-, 23. Ortho-, 9.

IV. Reaction of allyl bromide with the xylidines—



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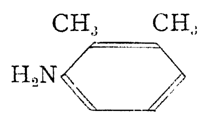

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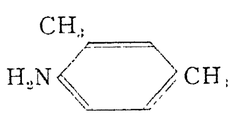

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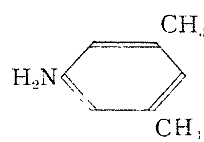

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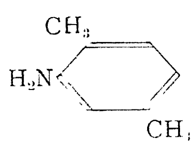

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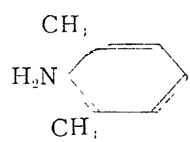
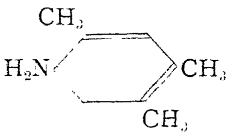


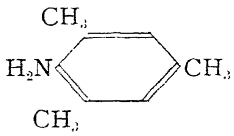
129.

[1] *Ber.*, **30**, 2966, 2775 (1897); *Jour. Russ. Phys. Chem. Soc.*, **29**, 444 (1897).

V. Reaction of allyl bromide with cumidine and mesidine—



174.



115.

The influence of the ortho-substituent is strongly marked in all these cases, with one very important exception—the nitro-compounds. In this connection it may be well to recall the fact that Baly and Collie[1] have shown that the introduction of a nitro-group into the benzene nucleus has the effect of altering the whole system of vibration of the benzene molecule and converting it into something which resembles an aliphatic compound. It appears probable that a study of the absorption spectra of the nitro-bromobenzenes would throw light upon Menschutkin's results.

A further series of investigations dealt with the reactions between allyl or methyl bromide and various primary amines. The following are the chief results:—

	Constants for CH_3Br	and for C_3H_5Br.
$NH_2.CH_3$	31910	8302
$NH_2.CH_2.CH_3$	——	3807
$NH_2.CH_2.CH_2.CH_3$	15215	3783
$NH_2.CH(CH_3).CH_2.CH_3$	5091	1200
$NH_2.C(CH_3)_3$	1822	314

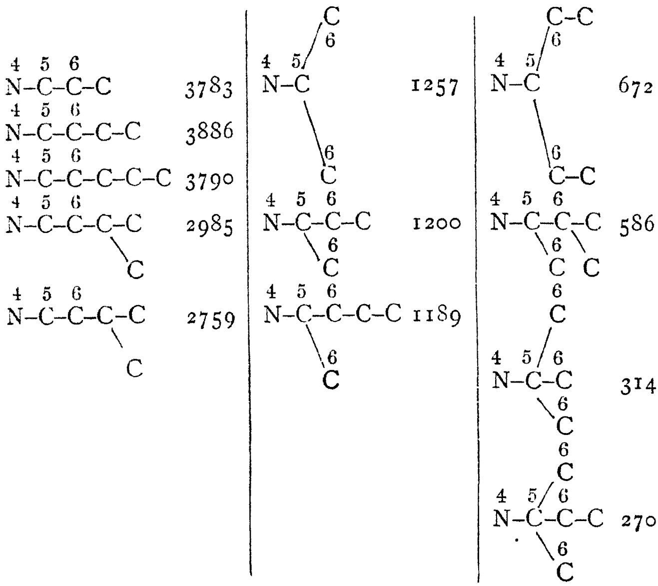
Now, in accordance with Bischoff's Dynamic Hypothesis, we should expect to find that in the case of amines and allyl bromide an accumulation of substituents at the carbon atom next the nitrogen one would hinder the progress of the reaction to the greatest extent; for this is the critical position in the compounds which would be produced by the reaction. This will be quite clear if we take a typical chain and number the atoms in it:—

$$\underset{1}{CH_2}:\underset{2}{CH}-\underset{3}{CH_2}-\underset{4}{N}-\underset{5}{C}\ldots$$

[1] Baly and Collie, *Trans.*, 87, 1332 (1905).

The experimental results support this, as can be seen from the last three figures in the second column.

The adverse influence of forking in the amine chain is shown by the following results, the numbers giving the positions in accordance with those above :—



In the remainder of this section we may examine the results of some other workers in the same field ; but as we shall have to describe more or less isolated facts it is necessary to arrange them in some order. It seems best to group the reactions under certain heads; and the simplest arrangement appears to be to class them according to the two atoms which are concerned in the actual junction of the two chains. We shall therefore consider the reactions in the following order: chain formation between two carbon atoms, between a carbon and a nitrogen atom, between a nitrogen atom and a non-carbon atom.

Bone and Sprankling[1] have studied the reactions between α-bromopropionic ester and the sodium derivatives of aceto-acetic ester, (IA), and methyl-acetoacetic ester, (IIA); as well as between α-bromo-isobutyric ester and the same sodium derivatives, (IB) and (IIB). The results are given by the figures below:—

	(IA.)	(IIA.)	(IB.)	(IIB.)
End of reaction	16 hours	17 hours	4 days	$2\frac{1}{2}$ days
Percentage of theoretical yield of ester	70%	52%	44%	18%
Percentage of theoretical yield of acid	42%	26%	18%	5%

The methylation of aceto-succinic ester, (III.), and its methyl derivatives, (IV.) and (V.), gave the following yields:—

(III.)

$$\begin{array}{l} CH_3.CO.CH.COOEt \\ \qquad\qquad\;\; | \\ \qquad\qquad CH_2.COOEt \end{array}$$

(IV.)

$$\begin{array}{l} CH_3.CO.CH.COOEt \\ \qquad\qquad\;\; | \\ \qquad CH_3.CH.COOEt \end{array}$$

(V.)

$$\begin{array}{l} CH_3.CO.CH.COOEt \\ \qquad\qquad\;\; | \\ \quad (CH_3)_2.C.COOEt \end{array}$$

	(III.) Per cent.	(IV.) Per cent.	(V.) Per cent.
Methylated product .	82·5	80	81·0
Methylated acid . .	14·0	26	10·5

In all these cases, true succinic acid derivatives were produced. The authors next examined the reactions of malonic ester, (VI.), with (a) bromopropionic ester, (b) bromo-isobutyric ester; and of methyl-malonic ester, (VII.), with (a) bromopropionic ester, (b) bromo-isobutyric ester. The result was in each case a mixture of two esters, which on hydrolysis gave succinic and glutaric acids:—

[1] Bone and Sprankling, *Trans.*, **75**, 839 (1899).

	Per cent. ester.	Succinic acid.	Glutaric acid.
(VIA.) $CH.(COOEt)_2$ / $CH_3.CH.COOEt$ and $CH.(CO.OEt)_2$ / $CH_2.CH_2.COOEt$	75	58	12·5
(VIB.) $CH(COOEt)_2$ / $(CH_3)_2.C.COOEt$ and $CH.(COOEt)_2$ / $CH_2.CH(CH_3).COOEt$	77	44	22
(VIIA.) $CH_3.C.(COOEt)_2$ / $CH_3.CH.COOEt$ and $CH_3.C.(COOEt)_2$ / $CH_2.CH_2.COOEt$	61	39	10
(VIIB.) $CH_3.C.(COOEt)_2$ / $CH_2.CH(CH_3).COOEt$	61	0	50

The reaction of α-cyano-propionic ester, (VIII.), with α-bromo-isobutyric ester gives rise to a mixture of trimethyl-succinic acid, (IX.), and dimethyl-glutaric acid, (X.), in the following proportions :—

(VIII.)

$$\begin{array}{l} CH_3.CH.COOEt \\ \quad | \\ \quad CN \end{array}$$

(X.)

$$\begin{array}{l} CH_3.CH.COOEt \\ \qquad | \\ \qquad CH_2.CH(CH_3).COOEt \end{array}$$

(IX.)

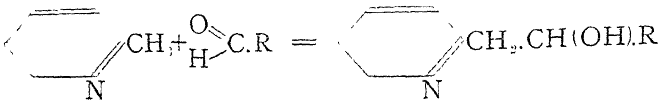
$$\begin{array}{l} \qquad CH_3.CH.COOEt \\ \qquad\quad | \\ (CH_3)_2.C.COOEt \end{array}$$

Total ester, 50–57%. IX. 15%. X. 25–30%.

It appears that in this case also the accumulation of substituents

in certain positions is so unfavourable to the course of some reactions that these take a different course and produce new products.

Aldehydes have the property of condensing with α- and γ-alkyl homologues of pyridine and quinoline in the manner shown by the equation :—[1]

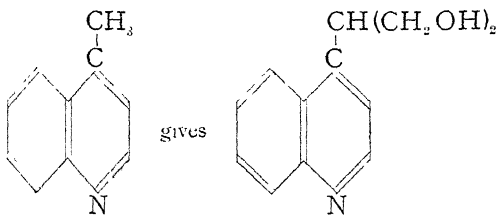


Konigs[2] has shown that when formaldeyde is used, all the three hydrogen atoms of the methyl group may be thus replaced, forming a radical of the type :—

$$-C{\begin{matrix} \diagup CH_2OH \\ -CH_2OH \\ \diagdown CH_2OH \end{matrix}}$$

This action, however, can take place only in those cases where there is no substituent in the ortho-position to the methyl radical. If such a substituent be present, one of the hydrogen atoms of the methyl radical loses its capacity for reacting with formaldehyde. Kónigs formulates the matter in the following way. In the α- or γ-methyl or methylene groups the number of hydrogen atoms which can be replaced by methylol groups is reduced by one if one of the neighbouring β-carbon atoms carries an alkyl group or belongs to a benzene nucleus (as is the case in lepidine, (I.)) :—

(I)

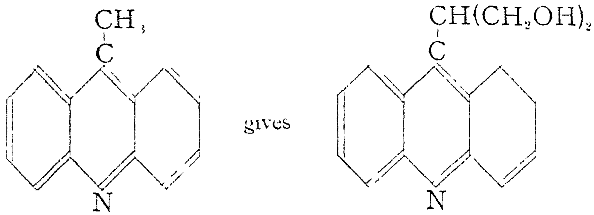


[1] Jakobsen and Reimer, *Ber.*, **16**, 1082, 2602 (1883).

[2] Konigs, *Ber.*, **31**, 2364 (1898) ; **32**, 223, 3599 (1899) ; **34**, 4323

On the other hand, even if the second β-position be occupied it appears to have no further hindering influence upon the reaction, for in *ms*-methyl-acridine, (II.), the same number of hydrogen atoms are replaced as in lepidine :—

(II)



The presence of a carboxyl group in the β-position appears to have an effect contrary to that of other substituents, as it facilitates the reaction.

As a final example in this branch of the subject we may choose the case of the triphenyl-methane dyes. The rosaniline dyes are obtained by oxidising a mixture of aniline with its homologues; and, in the case of para-rosaniline, the reaction may be represented thus :—

(I.)

$$NH_2.C_6H_4.CH_3 + 2O = NH_2.C_6H_4.CHO + H_2O$$

(II.)

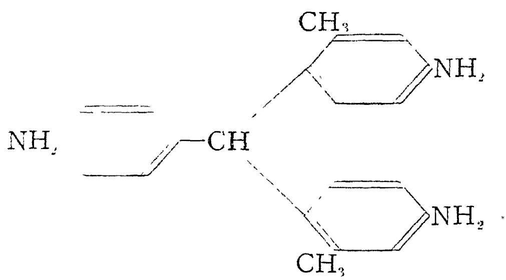
$$NH_2.C_6H_4.CHO + 2C_6H_5.NH_2 = NH_2.C_6H_4.CH\begin{matrix} / C_6H_4.NH_2 \\ \\ \backslash C_6H_4.NH_2 \end{matrix} + H_2O$$

Probably the *p*-toluidine employed is first oxidised to *p*-amidobenzaldehyde, as shown in the first equation, and this then condenses with aniline to form para-leucaniline. The hydrogen atom in the para-position to the amido-group of the aniline is

---

(1901); Konigs and Bischkopf, *Ber.*, **34**, 4327 (1901); Konigs and Stockhausen, Ber., **34**, 4330 (1901).

the one which is attacked in the course of the second reaction. Now, both the para-toluidine and the aniline can be replaced by their derivatives in this reaction without any hindrance being produced, except in one important case. When *m*-toluidine is substituted for aniline, the reaction is hindered to a very considerable extent, and the same is found when symmetrical xylidine, 1,3-dimethyl-5-amido-benzene, is used. Apparently, therefore, a hindrance is brought about by the presence of the methyl group in the meta-position to the amido-radical. If we write the formula of *o*,*o*-dimethyl-*p*-rosaniline in full, it will be seen that such methyl group will lie in the ortho-position to the hydrogen atoms which are replaced in the course of the reaction; and it appears probable that we are dealing with space influences in this case also :—

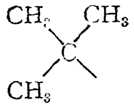


We must now turn to the second division of reactions, namely, those in which the chain is formed through a carbon and an oxygen atom. In this section we ought to have included ester formation, but it is more convenient to deal with that in a section by itself, instead of treating it as a branch of chain formation.

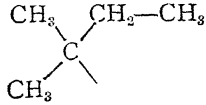
Spiegel and Sabbath[1] found that while alkyl-, allyl-, and benzyl-ethers of *p*-nitro-phenol could be prepared in the usual way, it was impossible to produce the ethers of tertiary butyl, (I.), or tertiary amyl, (II.). It was found that no hindrance existed in the case of the iso-butyl radical, (III.) :—

[1] Spiegel and Sabbath, *Ber.*, **34**, 1935 (1901).

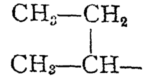
(I.)



(II.)



(III.)



Sagrebin[1] and, later, Rosenfeld-Freiberg,[2] have studied the course of the following reaction and measured the rates of ether formation in the case of several esters of benzene sulphonic acid :—

$$C_6H_5.SO_2.O.R + R.OH = C_6H_5.SO_2.OH + R.O.R$$

Rosenfeld-Freiberg's results are as follows :—

Benzosulphonic.	Methyl.	Ethyl.	Propyl.	Isobutyl.	Isoamyl alcohols.
Methyl ester	3019	1560	1137	772	827
Ethyl ester	2311	1130	816	498	546
Butyl ester	584	228	171	96	115
Isoamyl ester . . .	608	268	195	123	137

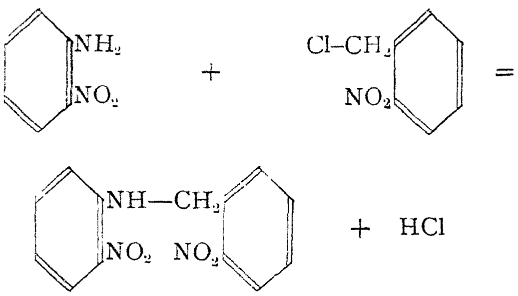
These results agree with those of Menschutkin as far as the influence of the side chain is concerned.

The next series of reactions with which we must deal includes those in which chain formation takes place through a carbon and a nitrogen atom. Oxime formation and similar reactions, being dealt with in a separate section, are not mentioned here.

Paal and Kromschröder[3] observed that when ortho-nitrobenzyl chloride was allowed to react with ortho-nitraniline, the yield of reaction product was very small; while if meta- or para-nitraniline were substituted for the ortho-compound, a much better yield was obtained. The influence of the nitro-group in the ortho-position is strongly marked, and appears to

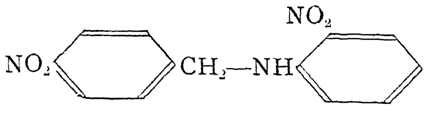
[1] Sagrebin, *J. Russ. Phys. Chem. Soc.*, **31**, 19 (1899).
[2] Rosenfeld-Freiberg, *ibid.*, **34**, 422 (1902).
[3] Paal and Kromschroder, *J. pr. Chem.*, [2] **54**, 265 (1896).

be sterical in character, since the two carbon atoms bearing the nitro-groups are in the 1,6-position to each other :—



The same authors found that a similar difference was noticeable in the behaviour of the reaction products; for *o*-nitrobenzyl-*o*-nitraniline could not be acetylated, while the corresponding meta- and para-nitraniline compounds showed no sign of hindrance.

Paal and Benker[1] examined the products of the action of *p*-nitrobenzyl chloride upon the three nitranilines and *o*-anisidine and found that all could be acetylated except *p*-nitrobenzyl-*o*-nitraniline, which agrees with the steric hypothesis :—

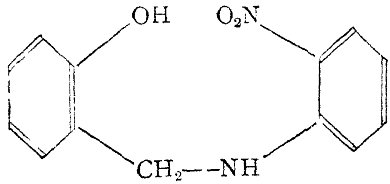


Paal and Hartel[2] have shown that when the three isomeric *o*-hydroxybenzyl-nitranilines are treated with acetic anhydride they behave in very different ways. The compound (I.) is acetylated on the hydroxyl group only, while in the other two the nitrogen is also attacked. The hindering influence of the

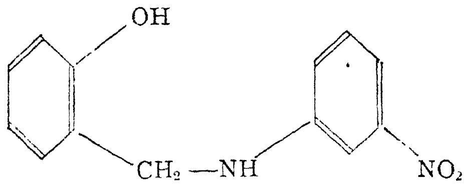
[1] Paal and Benker, *Ber.*, **32**, 1251 (1899).
[2] Paal and Hartel, *ibid.*, **32**, 2057 (1899).

nitro-group (which in (I.) lies in the 1,5-position to the entering acetyl group) is thus made evident:—

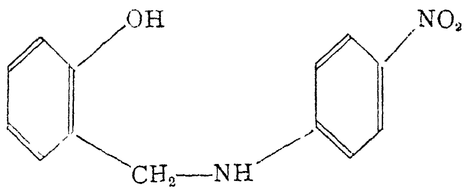
(I.)



(II.)



(III.)

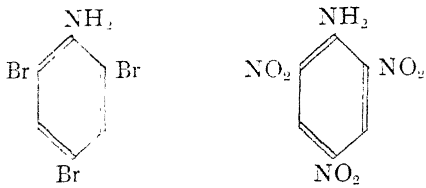


Aldehydes react with aniline and its homologues with the elimination of water in the following manner:—

$$X.CHO + H_2N–R = X–CH:N–R$$

Hantzsch[1] has found that symmetrical tribromo- and trinitro-aniline do not possess the property of reacting in this way. Here the bromine atoms would lie in the 1,6-position to the group R, were the reaction to take place.

[1] Hantzsch, *Ber.*, **23** 2776 (1890).



The effect of the ortho-substituents here recalls the influence of the same radicals in the case of the esterification of di-ortho-substituted aromatic acids.

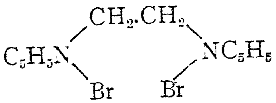
Eibner[1] measured the rise in temperature produced when equimolecular quantities of aniline and an aldehyde were mixed together. X represents the radical attached to the aldehydic group :—

X	Temperature rises to
H	over 100°
CH_3	,, 100°
C_2H_5	,, 100°
$(CH_3)_2CH$	59°
$(CH_3)_2CH.CH_2$	66°
C_6H_{13}	69°
C_6H_5	59°
$HO.C_6H_4$	55°

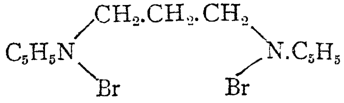
Flintermann and Prescott[2] endeavoured to join certain amido-compounds together by means of aliphatic dibromides. They found that two molecules of pyridine could be united by means of ethylene dibromide, giving the compound (I.), or trimethylene bromide, giving (II.); and that pyridine reacts better in this way than trimethylamine, which yields (III.) and (IV.). No chain could be formed by means of 1,2-dibromopropane, which ought to produce (V.) :—

[1] Eibner, *Annalen*, **316**, 99 (1901).
[2] Flintermann and Prescott, *Amer. Chem. J.*, **18**, 28 (1896).

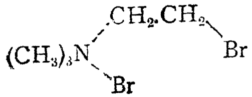
(I.)



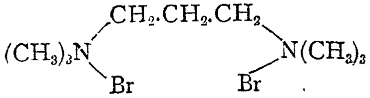
(II.)



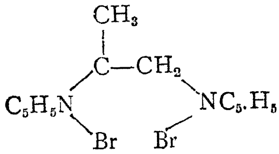
(III.)



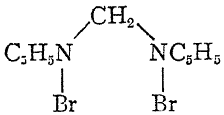
(IV.)



(V.)

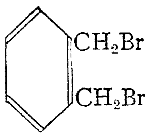


Baer and Prescott[1] prepared a methylene compound with pyridine :—



Bischoff[2] claims that this work supports his Dynamic Hypothesis; but it is rather difficult to see on what grounds he bases the claim.

Scholtz[3] carried out a research upon the reactions of *o*-xylylene bromide with amines :—



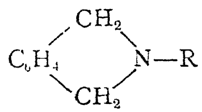
[1] Baer and Prescott, *Amer. Chem. J.*, **18**, 28 (1896).

[2] *Materialen*, p. 529.

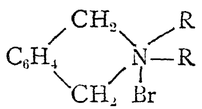
[3] Scholtz, *Ber.*, **31**, 420 (1898).

He found that the amido-compounds could thus be separated into six categories, the amines in each category reacting differently from those in the other classes :—

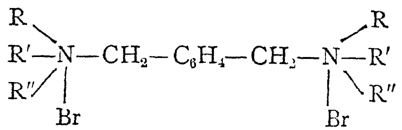
I. Primary *aliphatic* amines gave compounds of this type:—



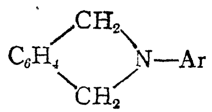
II. Secondary aliphatic amines react to form compounds like :—



III. Tertiary aliphatic amines give :—



IV. Primary *aromatic* amines, with no substituent in the ortho-position to the amido-group, give the following type, which, in contradistinction to the compound (I.), possesses *no* basic properties :—



V. When the primary amine has a substituent in the ortho-position to the amido group, the result is the type :—

$$Ar-NH-CH_2-C_6H_4-CH_2-NH-Ar$$

and the same occurs with secondary aromatic bases and mixed fatty-aromatic ones.

VI. When an aromatic base has two substituents in the ortho-position to the amido-group, no reaction at all occurs; and the same is the case with tertiary aromatic bases.

Wedekind[1] investigated the behaviour of picryl chloride with aromatic bases. He found that the nitro-group was the only one whose influence in the meta-position was very marked. This may be attributed to the effect, already described, which the nitro-group exerts upon the vibrations of the benzene nucleus. As regards the other substituents examined by Wedekind (COOH, Cl, OH, CH_3CO, CHO), all have most effect in the ortho-position to the amido-group, and least influence when in the para-position. The secondary bases, methyl-, ethyl-, benzyl-aniline, piperidine, diphenylamine, and carbazol were also dealt with. The first four gave the normal type of reaction product:—

$$\begin{array}{lll} X & & \\ & \diagdown & \\ & & N-C_6H_2(NO_2)_3 \\ & \diagup & \\ Y & & \end{array}$$

The purely aromatic bases, on the other hand, gave addition products of the type:—

$$\begin{array}{ccc} Ar & & C_6H_2(NO_2)_3Cl \\ & \diagdown \quad \diagup & \\ & NH & \\ & \diagup \quad \diagdown & \\ Ar & & C_6H_2(NO_2)_3Cl \end{array}$$

From a comparison between diphenylamine and methyl-aniline:—

$$\begin{array}{c} C_6H_5-N-C_6H_5 \\ | \\ H \end{array} \qquad\qquad \begin{array}{c} C_6H_5-N-CH_3 \\ | \\ H \end{array}$$

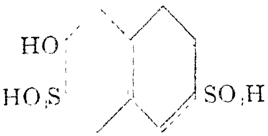
Wedekind deduces that in the former the hydrogen atom is sheltered from the approach of the chlorine atom by the heavy, slow-moving phenyl radical; whereas in methyl-aniline the

---

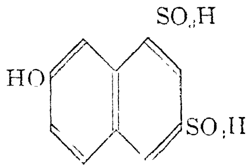
[1] Wedekind, *Ber.*, **33**, 426 (1900).

methyl group is easily pushed aside, and thus has less sheltering effect.

Two di-sulphonic acids of β-naphthol are known to which the following formulæ are ascribed :—



R-acid.



G-acid.

Smith[1] has studied the behaviour of these acids when brought into the presence of diazonium salts. It will be seen from the formulæ that, in the case of the G-acid, the hydrogen atom, usually replaced by the diazonium nucleus, lies between the hydroxyl and sulphonic groups; while in the case of the isomeric acid there is only one group, the hydroxyl, in the ortho-position. Smith mixed solutions of equal strength of the sulphonic acids with equal quantities of a solution of *p*-toluene-diazonium chloride, and estimated the amount of uncombined chloride after a fixed time had elapsed.

The following table gives the results obtained :—

Minutes.	Percentage of uncombined diazonium salt.	
	G-acid.	R-acid.
0	100·0	100·0
5	94·0	12·6
15	84·5	Nil
180	77·2	,,
24 hours	31·0	,,

It appears, therefore, that the sulphonic acid group produces a distinct hindering effect upon the reaction when it is

[1] Smith, *Trans*, **89**, 1505 (1906).

in the peri-position, but comparatively little effect when it is in the 2,6-position to the hydroxyl radical.

We now come to the final class of reactions in this section, viz. those in which chain formation is brought about by joining a nitrogen atom to some atom other than a carbon one. Very few facts seem to be known in this division.

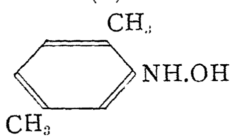
Lloyd and Sudborough[1] examined the formation of salts of organic bases with di-ortho-substituted benzene carboxylic acids in the hope of detecting some hindering effects. Nothing of the kind was observed.

Bamberger and Rising[2] found that ortho-substituents had considerable influence on the course of the reaction between aryl-hydroxylamines and nitroso-aryls :—

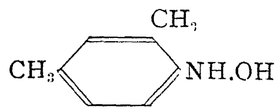
$$C_6H_5{-}NH{-}OH + O{:}N{-}C_6H_5 = C_6N_5{-}\underset{\diagdown\,O\,\diagup}{N{-}N}{-}C_6H_5 + H_2O$$

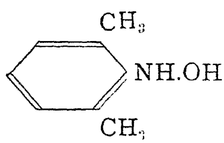
The results were as follows. Unmethylated or meta-methylated compounds react with almost the same ease; para-substitution reduces the reaction speed; ortho-substitution has most effect. The rate of reaction decreases in the following order :—

(I.)

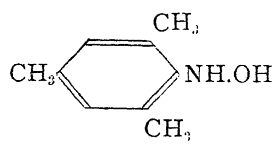


(II.)





(III.)



(IV.)

From the last compound, mesityl-hydroxylamine, no azoxy-derivative at all could be prepared.

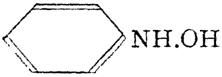
[1] Lloyd and Sudborough, *Trans.*, **75**, 580 (1899).

[2] Bamberger and Rising, *Annalen*, **316**, 257 (1901).

Bamberger and Rising[1] also examined the action of arylhydroxylamines upon diazobenzene chloride, and in this case also they found similar differences. The reaction normally follows the course of the equation :—

$$C_6H_5-\underset{\displaystyle OH}{\underset{|}{N}}-H + N{\equiv}\underset{\displaystyle Cl}{\underset{|}{N}}-C_6H_5 = C_6H_5-\underset{\displaystyle OH}{\underset{|}{N}}-N:N-C_6H_5 + HCl$$

The following figures give the relative amounts obtained by the authors in each case :—



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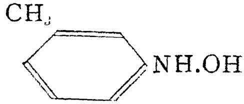

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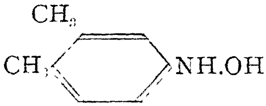

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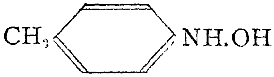

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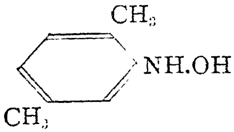

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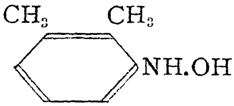

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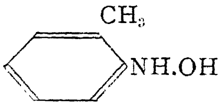

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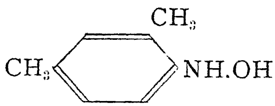

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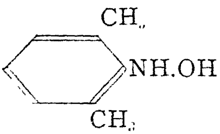

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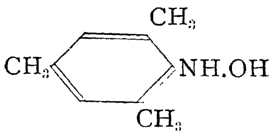

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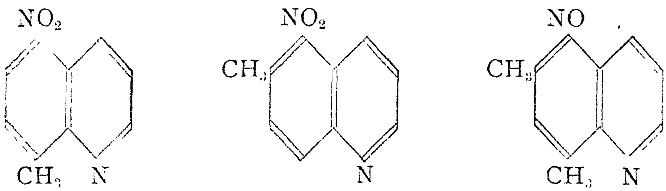
[1] Bamberger and Rising, *Annalen*, **316**, 257 (1901).

Here, also, very little action was obtained when mesityl hydroxylamine was used. It is noteworthy that Bamberger and Rust[1] found that mesidine shows a similar non-reactivity in the case of the diazo-reaction. They were unable to prepare its iso-diazo-derivative.

Elbs[2] has shown that in alkaline solution, electrolysis with a nickel electrode yields azoxy- and azo-derivatives in the case of *ana*-nitro-*o*-toluquinoline, (I.); *ana*-nitro-*p*-toluquinoline, (II.), and *ana*-nitro-*m*-xyloquinoline, (III.), yield only the corre sponding amido-quinolines :—



(I.) (II.) (III.)

It appears from a comparison of the formulæ that the substituent in the ortho-position to the nitro-group has a hindering influence on the reaction. Elbs considered this a case of steric hindrance

§ V. *INTRAMOLECULAR CHANGE.*

Hydrazobenzene, when acted on by mineral acids, undergoes an intramolecular change and is converted into benzidine:—

$$\underset{\text{Hydrazobenzene.}}{C_6H_5—NH—NH—C_6H_5} \longrightarrow \underset{\text{Benzidine.}}{NH_2—C_6H_4—C_6H_4—NH_2}$$

If azobenzene be reduced in acid solution, the hydrazobenzene thus formed undergoes change immediately, and the product of the reduction is benzidine and not hydrazobenzene.

A series of researches carried out by Jacobson and others,[3]

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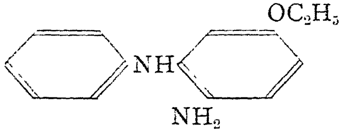
[1] Bamberger and Rust, *Ber.*, **33**, 3511 (1900).

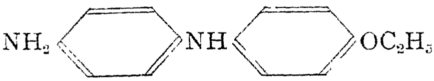
[2] Elbs, *Zeit. Electrochem.*, **10**, 579 (1904).

[3] Jacobson and others, *Ber.*, **25**, 992 (1892) ; **26**, 681, 688, 703 (1893) ;

with the object of finding the effect of substitution upon the reaction, led to the following results.

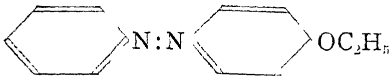
Jacobson began his investigation with *p*-ethoxy-azobenzene, expecting that on reduction it would break down into aniline and *p*-phenetidine, as the benzidine change was impossible, owing to the para-position being occupied by the ethoxy-group. No such decomposition occurred, however, but instead intramolecular rearrangement took place in two ways, the products being :—

(I.) 

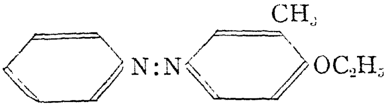
(II.) 

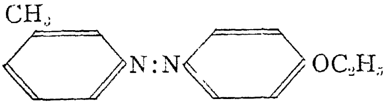
This change differs from the benzidine rearrangement, in that only one of the –NH– groups is converted into $-NH_2$; or, in other words, only half the benzidine change takes place. From this the change is called the *semidine rearrangement*, and its products are termed "semidines"; further, since in (I.) the two nitrogen atoms are in the ortho-position to one another, the substance is called an "ortho-semidine," and as in (II.) they are para to each other, that compound is a "para-semidine" derivative.

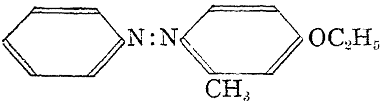
An examination of the relative quantities of the compounds formed from various azo-derivatives showed that great influence was exerted by the position of substituent groups in the two phenyl nuclei :—

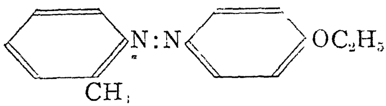
(I.) 

27, 2700 (1894); 28, 2541, 2680 (1895); *Annalen*, 287, 97 (1895); 303, 290 (1898); Witt and others, *Ber.*, 25, 1013 (1892); 27, 2351, 2358 (1894); Tauber, *ibid.*, 25, 1019 (1892); Noelting and Meyer, *Chem. Zeit.*, 18, 1095 (1894).

(II.) 

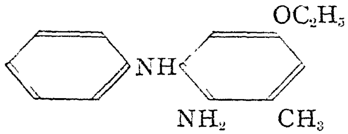
(III.) 

(IV.) 

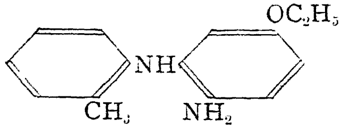
(V.) 

The compounds (I.), (II.), and (III.) gave on reduction chiefly ortho-semidines, and only very little of the para-semidine derivatives was produced; on the other hand, (IV.) and (V.) gave para-semidines as the chief reduction products. Many similar cases are known, all of which point to the fact that the ortho-semidine rearrangement does not take place to any considerable extent in those compounds which, in addition to the para-ethoxy-group, contain a substituent in the ortho-position to the azo-group in either nucleus. In other words, a substituent in either nucleus in the ortho-position to the azo-group hinders the ortho-semidine change. If, however, both para- and one ortho-position be substituted, there can be no question of the para-semidine rearrangement taking place, and, instead, the ortho-semidine change occurs, though to no great extent. The reason for this will be made clearer if we consider the products of an ortho-semidine change in compounds (IV.) and (V.). It is found that the wandering hydrogen atom always belongs to the ethoxylated nucleus, so the products are:—

(IV.)

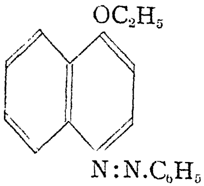


(V.)

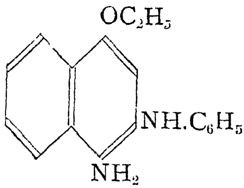


Now, in the case of (IV.), there are three substituents lying together on the one nucleus; while in (V.) the two nuclei have each a substituent ortho to the –NH– group. In this, Jacobson sees the reason why these changes occur only as minor reactions, there being too much space occupied by the amido- and methyl-groups to allow this type of rearrangement to occur easily.

An apparent anomaly is found in the case of a naphthalene derivative, (I.), which might be expected to produce more para-semidine than ortho-semidine, owing to the effect of the second benzene ring, part of which is in the ortho-position to the azo-group:—



(I.)

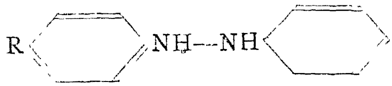


(II.)

In practice it is found that no such effect is noticeable; but that the chief product of the reaction is an ortho-semidine, (II.). According to Baeyer's view, a reduction of benzene to hexahydrobenzene tends to increase the space occupied by the molecule; so that the effect of the second benzene nucleus should be more marked after it is reduced. This proves to be the case, as only a small quantity of ortho-compound results,

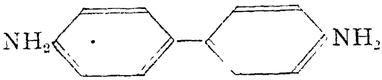
compared with a largely increased yield of a para-semidine derivative. The slight effect produced by the benzene ring, however, is a strange phenomenon, especially in the light of its influence in the case of esterification.

Jacobson found that a compound :—



gave rise to four different products :—

(I.)

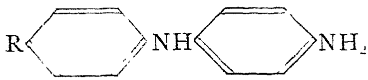


Change with elimination of R.

(II.)

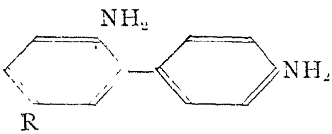
Ortho-semidine change.

(III.)



Para-semidine change.

(IV.)



Diphenyl formation without elimination.

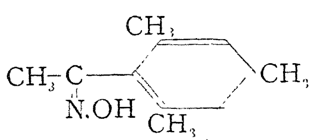
The comparative effect of various substituents is shown in the table below. A indicates that very little compound is formed; B that five to fifteen per cent. is produced; and C that considerable quantities are found :—

R	I.	II.	III.	IV.
Cl.	B	C	A	C
Br.	A	C	A	C
I.	(?)	B	o	C
$O.C_2H_5$	o	C	B	o
$O.CO.CH_3$	B	o	o	C
$N(CH_3)_2$	o	A	o	C
$NH.CO.CH_3$	o	o	C	o
CH_3	o	C	(?)	(?)
CO.OH	C	(?)	o	o

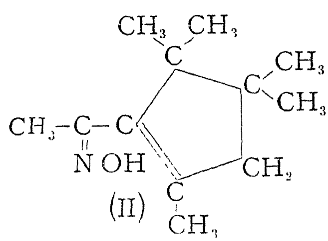
The difference between the effects of the alkyl and acyl substituents is especially noticeable.

A somewhat similar influence of an ortho-substituent was observed by Morgan.[1] In the case of the conversion of diazo-amido-compounds into amidoazo-derivatives, he found that a chlorine atom in the ortho-position to the diazo-group had a hindering influence.

Harries and Hubner[2] have studied the effect of methyl groups upon the Beckmann rearrangement. They found that in the oximes of acetomesitylene, (I.), desoxymesityl oxide, (II.), and camphor, (III.), the tendency to rearrange is greater than in the oxime of aceto-methyl-cyclopentene, (IV.). In (I.) and (III.) there are two methyl groups in the 1,5-position to the nitrogen, in (II.) there are three, but in (IV.) there is only one. The case therefore agrees with Bischoff's Dynamic Hypothesis:—



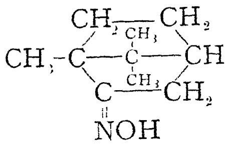
(I)



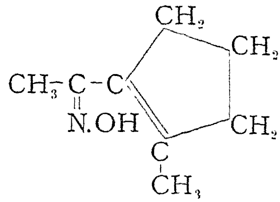
(II)

[1] Morgan, *Trans.*, **81**, 86 (1902).

[2] Harries and Hubner, *Annalen*, **296**, 302 (1897).



(III)



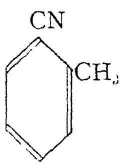
(IV)

§ VI. *ADDITION.*

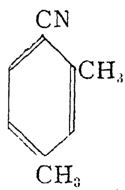
When a nitrile in alcoholic solution is treated with hydrochloric acid, the product of the reaction is a hydrochloride of an imido-ether, which is formed by the addition of one molecule of alcohol to the nitrile :—

$$R.CN + R'.OH + HCl = R.C{\overset{\displaystyle NH.HCl}{\diagup\!\!\diagup}}\!\!—OR'$$

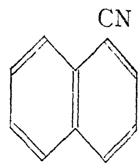
Pinner[1] found that, in the cases of the four following ortho-substituted nitriles, no addition of alcohol occurred :—



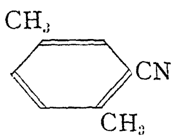
o-Tolunitrile.



2,4-Dimethyl-benzonitrile.



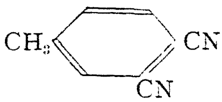
α-Naphthonitrile.



2,5-Dimethyl-benzonitrile.

[1] Pinner, *Ber.*, **23**, 2917 (1890); *Die Imidoäther und ihre Derivate*, Berlin (1892).

while in homophthalonitrile only one of the nitrile radicals is attacked :—



Rappeport[1] has shown that a nitro-group in the ortho-position can also hinder the formation of the addition product. This appears to be yet another instance in which the entrance of new atoms into the molecule is hindered by the presence of other radicals which are sufficiently near to occupy the space which the entering atoms would otherwise have filled.

Amidoximes can be formed by the action of hydroxylamine upon nitriles :—

$$CH_3.CN + NH_2OH = CH_3.\overset{\displaystyle NH_2 \atop /}{C}:N.OH$$

But examples of the hindering action of ortho-substituents are to be found in this reaction, just as in the case of the addition of water or alcoholates to the nitrile radical. The following examples may be quoted. Para- and meta-cyanobenzoic acid easily react with hydroxylamine, while the ortho-compound is only attacked after several days.[2] Para-tolunitrile is much more easily attacked than the ortho-isomer.[3] α-naphthonitrile[4] reacts like an ortho-substituted nitrile; while those compounds in which the cyano-group is shut in between two ortho-substituents show no faculty for amidoxime formation.[5] Para-methyl-ortho-nitro-benzonitrile is not attacked by hydroxylamine at temperatures lower than 100° C.[6]

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[1] Rappeport, *Ber.*, **34**, 1893 (1901).
[2] Muller, *ibid.*, **19**, 1491 (1886).
[3] Schubart, *ibid.*, **22**, 2433 (1889).
[4] Tiemann, *ibid.*, **22**, 2391 (1889).
[5] Kuster and Stallberg, *Annalen*, **278**, 207 (1894); *Ber.*, **22**, 2391 (1889).
[6] Weise, *Ber.*, **22**, 2418 (1889).

Under certain conditions, esters combine with alcoholates to form addition products :—

$$\begin{array}{ccc} OR'' & & OR' \\ R.C:O + NaOR'' & = & R.C—OR'' \\ & & ONa \end{array}$$

It has been observed by von Pechmann[1] that when benzoic ester is treated for half an hour with sodium methylate, 80 per cent. of addition product is formed, while with mesitylene carboxylic acid under the same conditions only 30 per cent. is produced at the end of six hours.

Angeli[2] has pointed out that the ease with which hydrocyanic acid is added on to ketonic compounds will depend upon the nature of the radicals attached to the carbonyl group. Victor Meyer[3] and Petrenko-Kritschenko[4] have shown that hexabromacetone has not the property of uniting with hydrogen cyanide. This may be due to steric hindrance; but it appears more probable that the chemical character of the chlorine atom plays a greater part.

The addition of bisulphites to ketones, according to the equation :—

$$KHSO_3 + R.CO.R' = \begin{array}{ccc} R & & OH \\ & \diagdown\diagup & \\ & C & \\ & \diagup\diagdown & \\ R' & & SO_3K \end{array}$$

has been studied by Petrenko-Kritschenko, and also by Stewart. The investigations of the former author were carried out with a view to determining the configuration of carbon chains, and will therefore be considered in Chapter IV., which deals with that subject. Some of his results, however, illustrate the hindering effect produced by an accumulation of substituents

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[1] von Pechmann, *Ber.*, **31**, 501 (1898).
[2] Angeli, *Atti R. Accad. Lincei*, [5] **5**, I., 84 (1896).
[3] V. Meyer, *Ber.*, **28**, 2777 (1895).
[4] Petrenko-Kritschenko, *ibid.*, **28**, 3203 (1895).

near the carbonyl group.[1] By mixing solutions of potassium bisulphite and a given ketone in such strengths as to produce a N/100 solution, leaving the mixture to stand for an hour, and then titrating the uncombined bisulphite with iodine, he arrived at the following results:—

		Per cent. bisulphite compound formed.
Acetone . . .	$CH_3.CO.CH_3$ . .	22
Methyl ethyl ketone .	$CH_3.CO.CH_2CH_3$.	14
Methyl isopropyl ketone	$CH_3.CO.CH(CH_3)_2$.	2·7
Acetophenone	$CH_3.CO.C_6H_5$ . . .	0·8
Methyl benzyl ketone .	$CH_3.CO.CH_2.C_6H_5$.	15·6

Stewart[2] made a similar investigation, using equal quantities of N/12 solutions of sodium bisulphite and the given ketone. Great care was taken to make the conditions uniform in all cases. The percentage results are shown in the following table:—

		10 mins.	30 mins.	50 mins.	70 mins.
Acetaldehyde	CH_3CHO	85	88	88·7	88·7
Acetone	CH_3COCH_3	28·5	47·0	55·9	58 9
Methyl ethyl ketone	$CH_3COCH_2CH_3$	14·5	25·1	32·4	38 4
Methyl isopropyl ketone	$CH_3COCH(CH_3)_2$	4·2	7·5	11·6	13·0
Pinacoline	$CH_3COC(CH_3)_3$	4·2	5 6	5·6	5 6

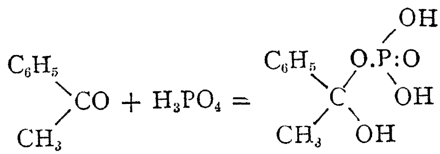
Now, in these cases it appears that the introduction of a substituent in the vicinity of the carbonyl group has the effect of decreasing the reactivity of the group in question. On the other hand, the carboxylic radical gives rise to anomalous effects, for, although it is larger than a hydrogen atom, its introduction appears to increase the reactivity of the carbonyl group near which it is introduced:—

	Per cent. 10 mins.	Per cent. 30 mins.	Per cent. 50 mins.	Per cent. 70 mins.
Acetone	28·5	47·0	55·9	58·9
Acetoacetic ester . . .	37·4	56·0	64·0	67·6
Acetonedicarboxylic ester	40·2	61·0	68·1	73·0

[1] Petrenko-Kritschenko, *Annalen*, **341**, 150 (1905).
[2] Stewart, *Trans.*, **87**, 186 (1905); *Proc.*, **21**, 78 (1905).

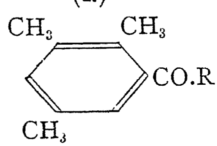
These results led Stewart and Baly[1] to make a series of further investigations, a summary of which was given in the introductory section of this chapter.

When certain ketones are treated with phosphoric acid, the two substances unite to form a compound which may be considered as a phosphoric ester of the unstable ortho-form of the ketone in question:—

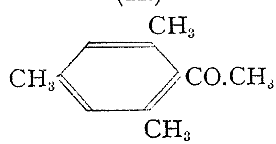


Klages and Lickroth[2] made a very complete investigation of the effect of substitution upon the reaction, and came to the following conclusions. In the aromatic series, no addition takes place when the acyl group lies between the two ortho-substituents. For instance, it was found that compounds of the type (I.) gave addition products easily; compounds like (II.) gave no reaction, while in (III.) only one carbonyl group reacted; though in (IV.) both were capable of forming an additive compound:—

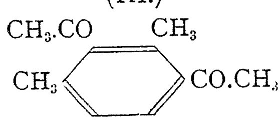
(I.)



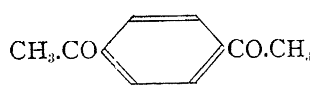
(II.)



(III.)



(IV.)



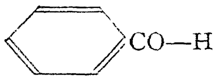
Fatty-aromatic ketones in which the aliphatic radical is

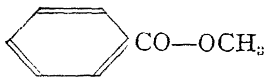
[1] Stewart and Baly, *Trans.*, **89**, 389 (1906).

[2] Klages and Lickroth, *Ber.*, **32**, 1549 (1899); compare Weiler, *ibid.*, 1908.

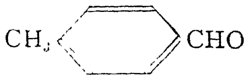
larger than methyl, usually form no oxonium salts. The only known exception seems to be propionyl-pseudocumenol ($2,4,5(CH_3)_3$-$1,C_2H_5CO.O.C_6H_2$), which gives a well-defined crystalline salt.

Raikow[1] studied the same phenomena in the case of the aldehyde series. He observed that while in the case of the aromatic ketonic compounds *one* ortho-substituent was sufficient to prevent the addition, in the case of the aldehydes *two* substituents are required. Further investigations made in conjunction with Schtarbanow[2] led to the following conclusions. Phosphoric acid or its esters will react with those compounds which contain a benzoyl group united with hydrogen or a methoxyl radical :—

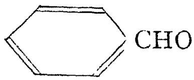




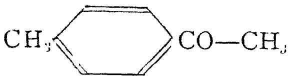
Substituents in the ring reduce the reactivity of the carbonyl group, having more effect in the case of the esters than with the aldehydes. No rule can be laid down, however, as even similar substituents in the same position appear to act differently, as can be seen from the examples below :—



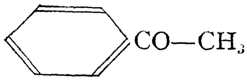
Reacts at once.



Reacts after a few days.



Unchanged.



Reacts at once.

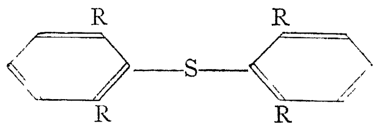
Raikow deduces that chemical reactions are influenced by two principal factors—the affinity between the reacting bodies, and the amount of "*reaction-sphere*" available. This second factor will depend upon the mutual relations of all the parts of the

[1] Raikow, *Chem. Zeit.*, **24**, 367 (1900).
[2] Raikow and Schtarbanow, *ibid.*, **25**, 1134 (1901).

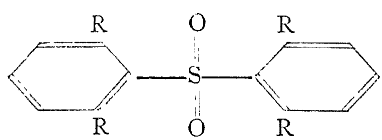
molecule. When a substance is melted or dissolved in a liquid a change takes place in the amount of reaction space available, and this suffices to bring about a change in the reactivity of the substance. He explains the fact that a long alkyl chain has more effect in the case of esters than in ketones by assuming that the valencies of the oxygen atom are asymmetrically placed, as shown in the formulæ below :—

Klages[1] has found that arsenious acid also has the faculty of forming addition compounds with ketones. The results are similar to those found in the case of phosphoric acid.

It has been observed by Blanksma[2] that the introduction of four substituents in the ortho-position to the sulphur atom has the effect of hindering the oxidation of a sulphide to a sulphone, *e.g.* compounds of the type shown below are not oxidised in the usual way :—



does not give :—



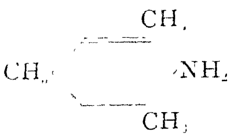
As a general rule, it is found that tertiary amines have the faculty of uniting with one molecule of an alkyl halide to form a quaternary ammonium salt, in accordance with the equation :—

[1] Klages, *Ber.*, **35**, 2313 (1902).
[2] Blanksma, *Rec. trav. chim.*, **20**, 425 (1901).

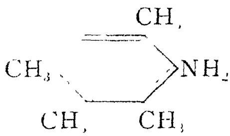
$$N.abc + Alk.X = N.abc\begin{smallmatrix}Alk\\ \\ X\end{smallmatrix}$$

In 1872, however, Hofmann[1] observed that no such addition compound was formed when mesidine, (I.), tetramethyl-amidobenzene, (II.), or pentamethyl-amidobenzene, (III.), was used as a starting-point.

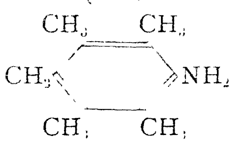
(I.)



(II.)

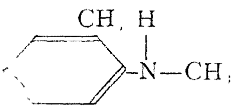


(III.)

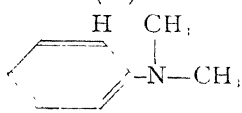


On the other hand, Rosenstiehl[2] showed that in certain cases an ortho-substituent could assist the formation of quarternary ammonium salts, even to the extent of causing a secondary amine to behave as a tertiary one. For example, he found that methyl-*o*-toluidine, (IV.), was able to react as if it were dimethyl-aniline, (V.), at least in so far as its power of combining with alkyl iodides was concerned.

(IV.)

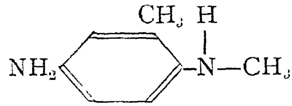


(V.)

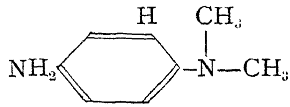


[1] Hofmann, *Ber.*, **5**, 704 (1872); **18**, 1824 (1885).
[2] Rosenstiehl, *Compt. rend.*, **115**, 180 (1892).

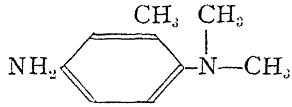
Other cases discovered by him were :—



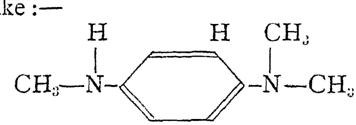
which reacts like :—



and :—



which reacts like :—



Rosenstiehl formulated the following rule: "A methyl group in the ortho-position to the nitrogen atom of a secondary amine confers upon it some of the properties of a tertiary nitrogen atom; it lends to a tertiary amine with free para-position the properties of a para-substituted amine; and to a para-amido-derivative of a tertiary amine it gives the properties of an asymmetrically alkylated diamine." It appears very probable that the proximity in space of the amido and methyl groups plays a considerable part in the question.

Fischer and Windaus[1] examined three bromo-toluidines and three bromo-xylidines, and found that (I.)—(V.) could be converted into quaternary ammonium iodides by repeated treatment with methyl iodide; (VI.), however, in which the amido group lies between two ortho-substituents, could not be made to yield the quaternary salt even on heating with methyl iodide to 100° C.[2]

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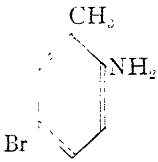
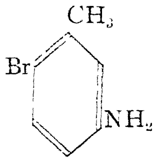
[1] Fischer and Windaus, *Ber.*, **33**, 1967 (1900).

[2] Friedlander, *Monatsh.*, **19**, 644 (1898).

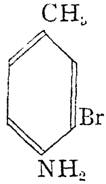
(I.)



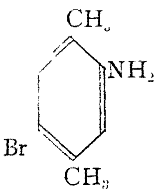
(II.)



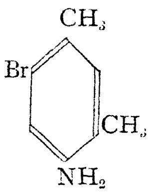
(III.)



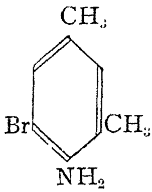
(IV.)



(V.)

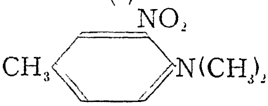


(VI.)

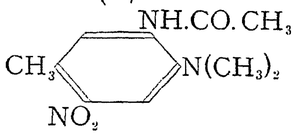


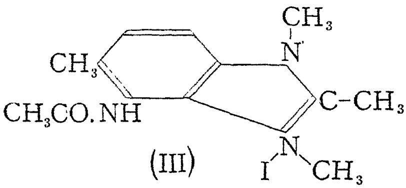
This lends considerable probability to the steric hindrance hypothesis; but some contradictions have been noted by Pinnow,[1] who finds that in several cases the steric influences are much weaker than other, probably purely chemical, ones. For example, neither (I.) nor (II.) gives an ammonium iodide, while (III.) gives an almost quantitative yield:—

(I)



(II)





(III)

Decker[2] has shown that in several cases those quinoline

[1] Pinnow, *Ber.*, **34**, 2077 (1901).

[2] Decker, *ibid.*, **24**, 1984 (1891).

derivatives which have a substituent in the ortho-position to the nitrogen atom do not give addition compounds with methyl iodide.

Wedekind[1] has studied the rate of formation of various quaternary ammonium salts, using alkyl iodides with dimethyl-aniline, and allowing the action to continue for forty-eight hours at ordinary temperatures. His results are as follows:—

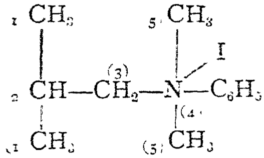
	Per cent. of theory.
CH_3I	89
$CH_3.CH_2I$	16[2]
$CH_3.CH_2.CH_2I$	28
$CH_3.CH_2.CH_2.CH_2I$	17
$(CH_3)_2CHI$	5
$(CH_3)_2.CH.CH_2I$	1
$\begin{matrix} CH_3 & \\ & CHI \\ C_2H_5 & \end{matrix}$	3
$CH_2{:}CH.CH_2I$	93[2]
$C_6H_5.CH_2I$	83

The comparatively low yield in the case of ethyl iodide is remarkable. It is also noteworthy that an illustration of Bischoff's Dynamic Hypothesis is to be found in the results of isobutyl and secondary butyl iodide. In the first case, the reaction product would be the dynamically unfavourable compound, (I.), in which the two pairs of methyl groups are in the 1,5-position to one another; while in the second case, (II.), though the bulky groups are actually nearer to each other in the chain, only three methyls are in the unfavourable position, instead of four:—

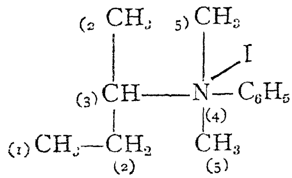
[1] Wedekind, *Ber.*, **32**, 511 (1899): *Zur Stereochemie d. Fünfwert. Stickstoffs*, p. 18

[2] Wedekind, *Annalen*, **318**, 90 (1901).

(I.)



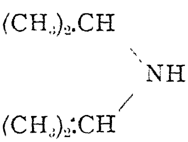
(II.)



In a later paper[1] Wedekind corrected some of his data, and added some new results. He allowed the alkyl iodides to stand with dimethyl-aniline for forty-eight hours, and then heated the mixture for two hours to 100° C. By this method he obtained the following figures :—

	Per cent. of theory
$CH_3.CH_2.CH_2I$	28
$CH_3.CH_2.CH_2.CH_2I$	17
$(CH_3)_2.CHI$	5
$(CH_3)_2.CH.CH_2.CH_2I$	3
$(CH_3)_2.CH.CH_2I$	1.5

These figures, however, are true only when the radicals are introduced by the method given above; for Wedekind confirmed the observation of Menschutkin[2] that a compound which was very difficult to synthesise by one method might be produced with ease if other derivatives were used as starting materials. For example, though in the first method above the yield with ethyl iodide and dimethyl-aniline amounted to only 16 per cent., an almost quantitative yield of the same end-product was obtained when methyl iodide and methyl-ethyl-aniline were allowed to combine. The effect of introducing a third forked chain into the molecule is very marked, as the following figures show :—

	With CH_3I	With $(CH_3)_2.CHI$
 Di-isopropyl-aniline.	45%	1·4%

[1] Wedekind, *Annalen*, **318**, 90 (1901)

[2] Menschutkin, *Ber.*, **28**, 1398 (1895)

$(CH_3)_2.CH.CH_2.CH_2$

$\quad\quad\quad\quad\quad\quad\quad\quad\quad\diagdown$

$\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad NH \quad\quad\quad 47\%$

$\quad\quad\quad\quad\quad\quad\quad\quad\quad\diagup$

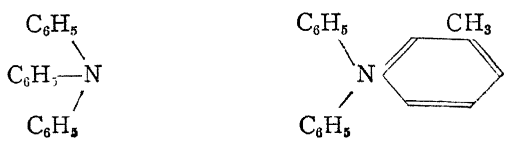
$(CH_3)_2.CH.CH_2.CH_2$

Di-iso-amyl-aniline.

The fact that di-isoamyl-aniline reacts with methyl iodide with ease stands in strong contrast to the difficulty with which di-isopropyl-aniline is acted on by isobutyl iodide, though in the former case a compound is formed which is richer in carbon atoms than in the latter. It is thus evident that the *position* of the atoms has much more influence than their number.

Häussermann[1] observed that methyl iodide had no action upon either triphenylamine, (I.), or diphenyl-*m*-toluidine, (II.), even when the two substances were heated together in a sealed tube for ten hours at a temperature of 100° C.

(I.) (II.)



It is possible to explain this on steric grounds, though chemical influences alone might suffice.

From this evidence, it seems fairly deducible that space considerations play no small part in the addition reactions of tertiary bases; but it may be well to direct attention to the anomalies which have been mentioned incidentally. It is probable that in some such abnormal reactions may be found the key to other and wider applications of stereochemistry.

§ VII. *SUBSTITUTION.*

We must now turn to deal with the effect of steric influences upon substitution reactions, in many of which an

[1] Häussermann, *Ber.*, **34**, 38 (1901).

unstable addition compound seems to be the first product of the reaction.

When phosphorus pentachloride is allowed to react with a ketone, it generally replaces the oxygen atom by two atoms of chlorine :—

$$\begin{array}{l} R \\ \quad\diagdown \\ \quad\;CO \\ \quad\diagup \\ R' \end{array} + PCl_5 = \begin{array}{l} R \\ \quad\diagdown \\ \quad\;CCl_2 \\ \quad\diagup \\ R' \end{array} + POCl_3$$

But in some cases this reaction can be hindered, or even completely prevented, by the presence of other groups of atoms near the carbonyl radical. Fittig and Borsche[1] observed that unsymmetrical dichloracetone did not react in the cold with phosphorus pentachloride; and even heating the two substances together did not produce any marked effect. Faworsky[2] noted a somewhat similar effect in the case of α-dichloropropyl-methyl ketone, $CH_3.CO.CCl_2.CH_2.CH_3$, no action being noticeable, even after the mixture had been raised to the boiling-point. It therefore seems to be the case that two chlorine atoms in the α-position to a carbonyl group have a hindering effect on the reaction; but it cannot be asserted that the hindrance is purely stereochemical in nature, as it may be due to the chemical influence of the chlorine atoms.

Pechmann and Burton[3] found that acetone-dicarboxylic ester reacted readily with pentachloride of phosphorus, in the following way :—

$$\begin{array}{l} \;\diagup CH_2.COOR \\ CO \\ \;\diagdown CH_2.COOR \end{array} + PCl_5 = \begin{array}{l} \;/\!\!/ CH.COOR \\ C.Cl \\ \;\diagdown CH_2.COOR \end{array} + HCl + POCl_3$$

When Petrenko-Kritschenko[4] attempted to repeat this reaction, with substituted esters, he found considerable difficulty. Trialkylated acetone-dicarboxylic esters react only with

[1] Fittig and Borsche, *Annalen*, **133**, 114 (1865).
[2] Faworsky, *J. pr. Chem.*, [2] **51**, 536 (1895).
[3] Pechmann and Burton, *Ber.*, **20**, 145 (1887).
[4] Petrenko-Kritschenko, *Annalen*, **289**, 52 (1895).

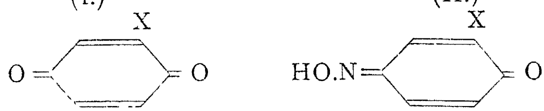
difficulty, and when the substitution is carried a step further and tetralkylated esters used, no action could be produced. Dibenzyl-acetone-dicarboxylic esters show a similar character, since they do not react with phosphorus pentachloride even at water-bath temperature. In these instances it would seem that the hindrance is more probably due to stereochemical than to purely chemical causes, as such an introduction of alkyl groups into a compound does not usually exercise much effect on the chemical nature of the substance.

The case of oxime formation has long been considered to be the classic example of steric effects upon chemical reactions. The chief worker in this field has been Kehrmann,[1] who has studied the question as it concerns substituted quinones. The results arrived at by him and other workers[2] in the same field may be summarised as follows :—

(1). When ordinary *p*-benzo-quinone is allowed to act with a sufficient quantity of hydroxylamine, it yields a dioxime, both carbonyl groups being attacked.

(2). In the case of mono-substituted *p*-benzo-quinones it is usually found that at first only one carbonyl group reacts, and that thus a monoxime is produced. The substituent group appears to exercise a shielding influence upon the carbonyl group in the ortho-position. For example, in the case (I.) below, where X is chlorine, bromine, or methyl, only the oxime (II.) is formed at first, and a dioxime is produced with some difficulty :—

(I.) (II.)



(3). Di-substituted quinones can be divided into two classes: (*a*) those in which the two substituents are in the ortho-position

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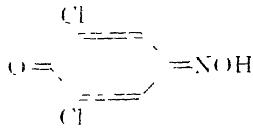
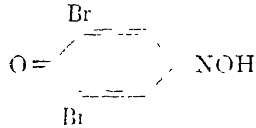
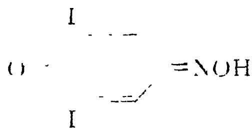
[1] Kehrmann, *Ber.*, **21**, 3315 (1888) ; **23**, 3557 (1891) ; **27**, 1431, 3344 (1895) ; *J. pr. Chem.*, [2] **40**, 257 (1889) ; **42**, 134 (1890) ; *Annalen*, **310**, 89 (1900).

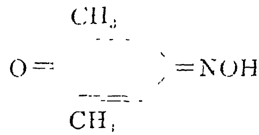
[2] Herzig and Zeisel, *Ber.*, **21**, 3403 (1888); Nietzki and Schneider, *ibid.*, **27**, 1431 (1894) ; Bornstein, *ibid.*, **34**, 4349 (1901).

to the carbonyl group; and (*b*) those in which each carbonyl group has one ortho-substituent. In class (*a*) many instances may be quoted to show that hydroxylamine attacks only the carbonyl group which is free from ortho-substituents, *e.g.* the following monoximes are produced:—

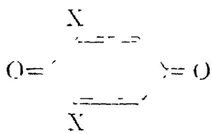




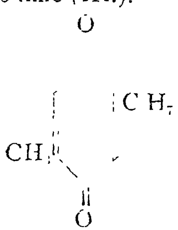




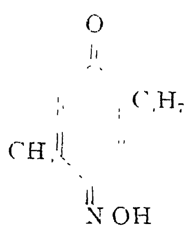
In general it is found that in the case of an oxime of the type —



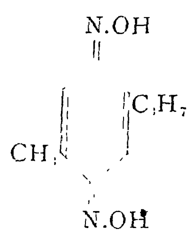
the difficulty of producing a dioxime is greater when X is an atom of chlorine, bromine, or iodine, than when it is a methyl or ethyl group. In class (*b*) a new factor in the problem becomes apparent. The case of thymoquinone will serve as an example. When this substance, (I.), is treated with hydroxylamine it yields in the first instance the monoxime (II.), and only with some difficulty can it be converted into the dioxime (III.).



(I.)



(II.)

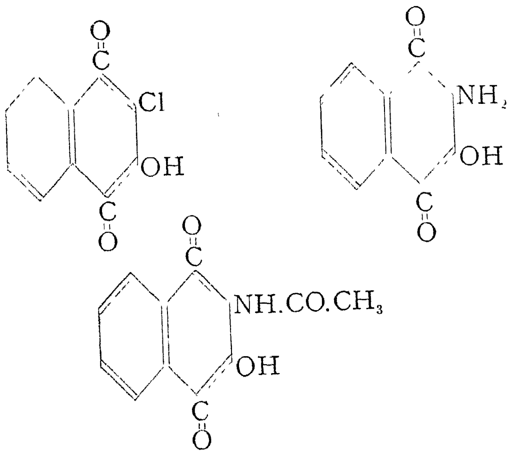


(III.)

Kehrmann, from this, deduced that the progress of the substitution reaction was influenced by the atomic and molecular bulk of the substituents; since oxime formation takes place first at the carbonyl group which has the smaller ortho-substituent.

(3). Tri-substituted quinones show a somewhat similar behaviour; the carbonyl group with two ortho-substituents is less easily attacked than the other. When some of the substituents are alkyls and the others halogen atoms, is is found that oxime formation is more easily carried out the fewer halogen substituents there are present; no oximes of trihalogen quinones can be produced, while *m*-dihalogen-alkyl-quinones easily yield somewhat unstable oximes, and mono-halogen-thymoquinones can at once be converted into oximes.

(4). Tetra-substituted quinones give no oximes; with the exception of naphthoquinones such as :—

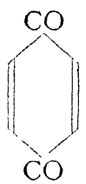


In this case the slight effect of the second benzene nucleus recalls the analogous case of the benzidine rearrangement,* where also it has little action.

* See p. 396

Stewart and Baly[1] have thrown doubt upon the correctness of Kehrmann's assumptions as to the cause of the non-reactivity of the carbonyl group. As has already been explained in the introductory section of this chapter, these authors proved that the reactivity of a carbonyl group in any ketonic compound was proportional to the persistence of a certain absorption band in the spectrum of the substance. An examination of the spectra of various quinonoid compounds yielded the following results. (1) Benzoquinone has an isorropic * band of long persistence, and shows no sign of benzenoid character; (2) the introduction of methyl radicals or halogen atoms tends to diminish the persistence of the isorropic band and to produce in the spectrum a benzenoid band, the change being greater with chlorine than with methyl; (3) the benzenoid character of the compound is intensified in proportion to the decrease of the isorropic band. From these facts the following conclusions were drawn. Benzoquinone exists almost entirely in the quinonoid form. Toluquinone, while existing to a great extent in the quinonoid form, possesses certain characteristics of benzene, and probably oscillates in a manner similar to that in which the benzene molecule vibrates. Chloro-benzoquinone, although still possessing certain quinonoid properties, is in a state of vibration approximating more closely to the intramolecular motions of benzene. Trichloro-quinone, in which the isorropic process is practically non-existent, vibrates in a manner almost identical

* The "isorropic band" is one found in the spectra of compounds which contain either of the groupings :—

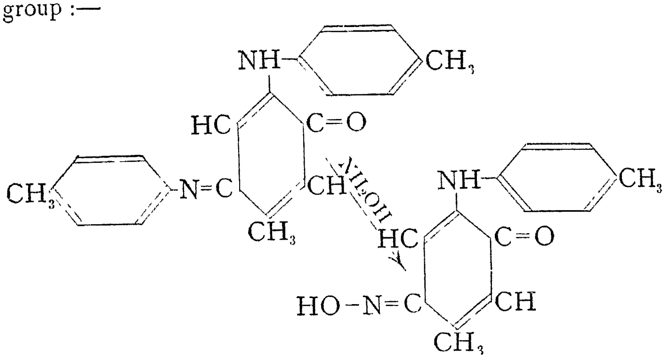
—CO.CO— or 

and having its head situated approximately at 2000 units (Stewart and Baly, *Trans.*, **89**, 489 (1906).

[1] Stewart and Baly, *ibid.*, **89**, 618 (1906).

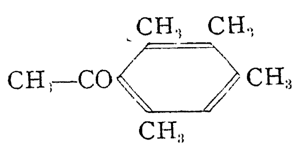
with the benzene ring vibration. In another paper, these authors[1] had shown that in order to bring about the isorropic process, the quinonoid structure had first to be produced. As the reactivity of the carbonyl group in quinones depends upon the isorropic process, it is evident that the benzenoid character of the substituted quinones is in itself sufficient to explain their non-reactivity without recourse being had to the steric hindrance hypothesis.

A peculiar case of oxime formation was observed by Bórnstein,[2] who showed that when hydroxylamine reacts with *p*-tolyl-amido-*p*-toluquinone-monotolyl-imide, it does not attack the carbonyl group, but instead drives out the tolyl-imido group :—



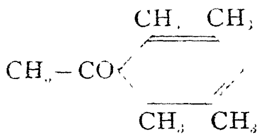
He attributes this to the steric hindrance caused by the tolyl-amido group in the ortho-position to the carbonyl radical.

In the case of ketones whose carbonyl groups do not form part of a ring, many similar examples of hindrance have been observed. Claus and Stiebel[3] showed that aceto-durol :—

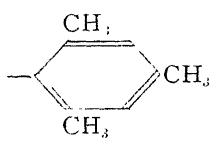


[1] Stewart and Baly, *Trans.*, **89**, 489 (1906)
[2] Bornstein. *Ber.*, **34**, 4349 (1901).
[3] Claus and Stiebel, *ibid.*, **20**, 3101 (1887).

could not be converted into an oxime, though there appears to be some doubt in the case of aceto-isodurol [1]. —



Beckmann [2] found that benzpinacoline, $C_6H_5.CO.C(C_6H_5)_3$, gives no oxime, nor does phenyl-mesityl ketone [3] react, even at high temperatures, with hydroxylamine. Feith and Davies [4] showed that at low temperatures no reaction takes place between acetomesitylene and hydroxylamine; while if the temperature be raised, the resulting compound is not the oxime, but a product of the Beckmann change. Baum [5] examined the cases of dibenzoylmesitylene, diaceto-isodurol, and acetopentamethylbenzene, none of which reacted with hydroxylamine. Mesitylglyoxylic acid gave a nitrile; and acetomesitylene an amido-derivative. V. Meyer [6] carried out a series of investigations of the mesitylene derivatives, and found that no oxime was formed by the following nine ketones, in whose formulæ M represents the radical :—



$M.CO.CH_3$	$M.CO.C_2H_5$	$M.CO.C_3H_7$ (normal and iso)
$M.CO.C_6H_5$	$M.CO.CH_2Cl$	$M.CO.CHCl_2$
$M.CO.CCl_3$	$M.CO.CH_2CH_2COOH$	

Smith [7] could produce no oxime from xylyl-*o*-tolyl ketone.

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[1] Claus and Focking, *Ber.*, **20**, 3098 (1887); Baum, *ibid.*, **28**, 3207 (1895); V. Meyer and Sohn, *ibid.*, **29**, 830, 2564 (1896).

[2] Beckmann, *Annalen*, **252**, 14 (1889).

[3] Hantzsch, *Ber.*, **23**, 2772 (1890).

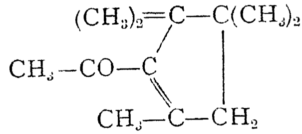
[4] Feith and Davies, *ibid.*, **24**, 3546 (1891).

[5] Baum, *ibid.*, **28**, 3207 (1895).

[6] V. Meyer, *ibid.*, **29**, 836 (1896)

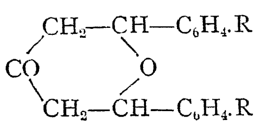
[7] Smith, *ibid.*, **24**, 4050 (1891).

All the above cases seem clearly to show the effect of space influences upon the chemical behaviour of the compounds; in most of them it appears probable that the methyl groups situated in the ortho-position in the carbonyl radical exert a hindering effect upon the reactivity of the latter. When other ketonic compounds are considered, the same influences may be traced. For example, Harries and Hubner[1] found difficulty in oxime formation in the case of the ketone:—

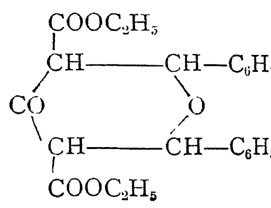


Petrenko-Kritschenko and Rosenzweig[2] noticed that in the case of certain tetrahydropyrone derivatives, oximes were not formed. They showed that in compounds of the type (I.), where R in the ortho-position was either a methoxyl or an ethoxyl group, no hindrance was noticeable; but no oximes could be produced from either (II.) or (III.):—

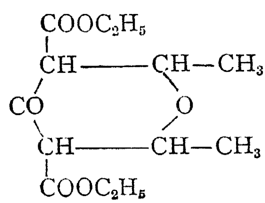
(I.)



(II.)



(III.)



[1] Harries and Hubner, *Annalen*, **296**, 301 (1897).
[2] Petrenko-Kritschenko and Rosenzweig, *Ber.*, **32**, 1747 (1899).

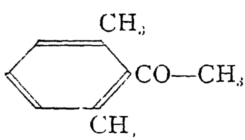
The fact that unreduced pyrone derivatives do not form oximes can hardly be counted as an example of steric hindrance; this case seems to find a much better explanation in the formula for pyrone put forward by Collie.[1]

Petrenko-Kritschenko[2] has studied quantitatively the action of hydroxylamine upon various ketones; his results will be dealt with in Chapter IV.

Stewart[3] made some investigations on the effect upon oxime formation of introducing substituents into certain ketonic compounds. Among the figures given by him are the following:—

Ketone.	Formula	10	20	30	40 minutes.	
Acetone . .	CH_3COCH_3	45·1	49·7	50	50·1	oxime formed.
Methyl ethyl ketone	$CH_3COCH_2CH_3$	36·0	39·2	39·2	39·2	,,
Methyl iso-propyl ketone	$CH_3COCH(CH_3)_2$	31·4	31·5	32·0	32·0	,,
Pinacolin . .	$CH_3COC(CH_3)_3$	12·9	17·0	24·5	24·5	,,

It has been found that in the case of some ketones, a hindrance to the formation of hydrazones can be detected which is similar to that found in the case of oxime formation. The effect is most marked in the aromatic compounds; for instance, ketonic compounds of the type:—



do not react with phenylhydrazine[4]; but, in some cases, when

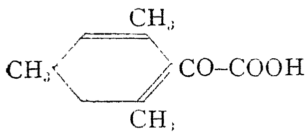
[1] Collie, *Trans.*, **85**, 971 (1904).

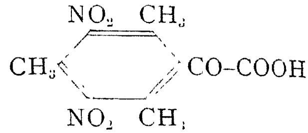
[2] Petrenko-Kritschenko, *J. pr. Chem.*, [2] **61**, 431 (1900); *Ber.*, **34**, 1702 (1901); **39**, 1452 (1906).

[3] Stewart, *Trans.*, **87**, 410 (1905).

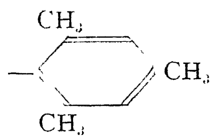
[4] Baum, *Ber.*, **28**, 3207 (1895); V. Meyer, *ibid.*, **29**, 835 (1896).

another group is substituted for the methyl of the acetyl radical, the capacity of hydrazone formation returns to the ketone. Examples of this are mesityl-glyoxylic acid (I.), and its dinitro-derivative (II.) :—


(I.)


(II.)

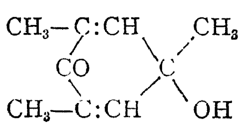
This is probably due to some change in the chemical nature of the compound brought about by the introduction of the new group. V. Meyer and Kullgren[1] studied the effect of various side-chains attached to a mesityl nucleus, and found that the following compounds did not react with phenylhydrazine. In the formulæ, the mesityl radical :—

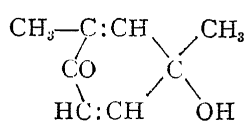


is represented by M :—

$$M.CO.CH_2.Cl$$
$$M.CO.CH.Cl_2$$
$$M.CO.C.Cl_3$$
$$M.CO.CH_2.CH_2.COOH$$

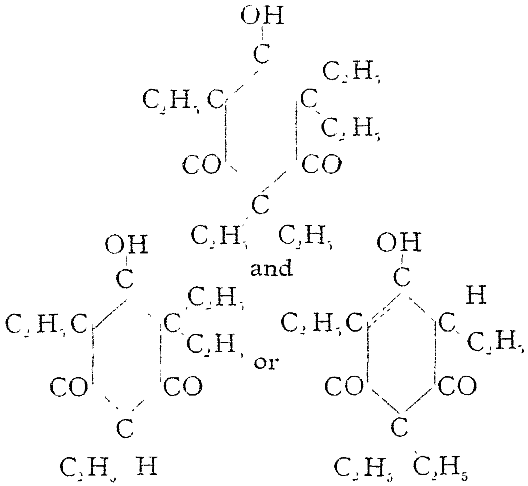
Bamberger and Rising[2] found that aryl-hydrazines had no action on mesityl-quinol, (I.), though the lower homologue, (II.), reacted with them :—


(I.)

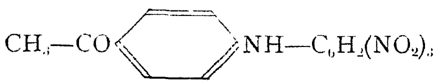

(II.)

[1] V. Meyer and Kullgren, *Ber.*, **29**, 836 (1896).
[2] Bamberger and Rising, *ibid.*, **34**, 3636 (1901).

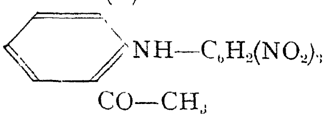
Herzig and Zeisel[1] found that neither penta- nor tetra-ethyl-phloroglucinol formed a hydrazone :—



Wedekind,[2] in studying the action of picric chloride on aromatic bases, observed that though the compound (I.) formed a hydrazone with ease, the substance (II.) could not be induced to react at all :—



(I.)



(II.)

Somewhat similar effects have been noticed in the open-chain ketones, though in their case the hindrance is not so strongly marked.

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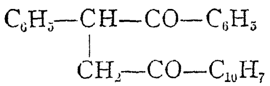
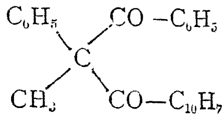
[1] Herzig and Zeisel, *Ber.*, **21**, 3493 (1888).
[2] Wedekind, *ibid.*, **33**, 426 (1900).

Petrenko-Kritschenko, Pissarchewsky, Herschkowitsch, and Ephrussi[1] found that phenylhydrazine reacts with the mono-methyl- and mono-ethyl-acetone-dicarboxylic ester; but has no action on the dimethyl and diethyl derivatives. In this case the introduction of the alkyl groups is sufficient to produce hindrance, which is shown also in the case of the 1,4-diketones which have been studied by Smith and MacCoy.[2] They noticed that while phenyl hydrazine easily converts desyl-*p*-acetophenone, (I.), into a pyridazine derivative, it has no effect on the *α*-isomer, (II.), nor does it act upon desyl-acetomesitone, acetomesitylene, benzoylmesitylene, dibenzoylmesitylene, or propionyl-isodurol.



(I.)



(II.)

Petrenko-Kritschenko and Eltschaninoff[3] have made a quantitative examination of the velocity with which phenyl-hydrazine reacts upon certain ketones. The following figures giving relative velocities are relevant to the present question:—

Acetone	66
Methyl ethyl ketone . .	52
Methyl-*n*-propyl ketone . . .	38
Acetonylacetone	22·7

When pentachloride of phosphorus and benzoic acid are allowed to interact, benzoyl chloride is produced; but if a hydroxy-benzoic acid be used, it forms a phosphorus derivative,[4] thus—

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[1] Petrenko-Kritschenko, Pissarchewsky, Herschkowitsch and Ephrussi, *Ber.*, **28**, 3203 (1897).

[2] Smith and MacCoy, *ibid.*, **35**, 2171 (1902).

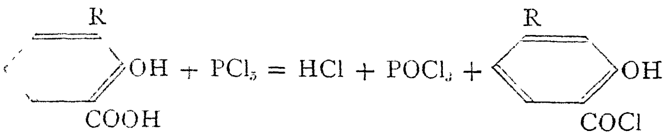
[3] Petrenko-Kritschenko and Eltschaninoff, *Annalen*, **341**, 150 (1905).

[4] Anschutz and Moore, *ibid.*, **228**, 308 (1885); **239**, 314, 333 (1887).

$$C_6H_4\begin{smallmatrix}OH\\ \end{smallmatrix}-COOH + PCl_5 = HCl + POCl_3 + C_6H_4\begin{smallmatrix}OH\\ \end{smallmatrix}-COCl$$

$$C_6H_4\begin{smallmatrix}OH\\ \end{smallmatrix}-COCl + POCl_3 = HCl + C_6H_4\begin{smallmatrix}O.POCl_2\\ \end{smallmatrix}-COCl$$

Anschutz and his students[1] have shown that the reaction follows this course only when there is no substituent in the ortho-position to the hydroxyl group. Should such a substituent be present, the reaction takes the course shown below, the phosphorus oxychloride having no action:—



Anschutz has shown that the action takes place thus in the case of the following substances:—

3-Methyl-salicylic acid.	3,5-Dinitro-salicylic acid.
3-Chloro-salicylic acid.	3-Nitro-5-chlorosalicylic acid.
3-Nitro-salicylic acid.	3-Nitro-5-bromo-salicylic acid.
3,5-Dichloro-salicylic acid.	3-Bromo-5-nitro-salicylic acid.
3,5-Dibromo-salicylic acid.	Hydroxy-uvitic acid.
3,5-Di-iodo salicylic acid.	α-Hydroxy-β-naphthoic acid.

It seems probable that the phosphorus addition product occupies a certain amount of space, and that there is not sufficient room for it to form if the hydroxyl group is surrounded by other atoms, as it will be when the two ortho-positions are occupied by radicals.

One of the earliest cases of hindrance in the reaction of anilide formation was noticed by Bischoff and Walden,[2] who

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[1] Anschutz and others, *Ber.*, **30**, 221 (1897).

[2] Bischoff and Walden, *ibid.*, **23**, 1972 (1890); **25**, 2919, 2931, 3275 (1892); **26**, 265 (1893).

found that the introduction of methyl and acyl radicals hindered the formation of piperazine derivatives. Bischoff[1] next investigated the rate of formation of various anilides at a temperature of 100° C., according to the equation—

$$X.COOH + H_2N.C_6H_5 = H_2O + X.CO.NH.C_6H_5$$

He found the following percentages of anilide formed in equal times:—

X	Per cent	X	Per cent.	X	Per cent.
H	97	C_6H_5	0	$HO.CH_2$	41·4
CH_3	19·4	C_6H_5CH	0	$HO.CH(CH_3)$	28·5
C_2H_5	16·0	$C_6H_5CH_2CH_2$	0	$HO.CH(C_2H_5)$	20·9
n-C_3H_7	6·5	$C_6H_5CH{:}CH$	0	$HO.CH(C_6H_5)$	16·2
n-C_4H_9	5·4			$HO.C(CH_3)_2$	7·1
$(CH_3)_2CH$	4·4				
$(CH_3)_2.CH.CH_2$	0·0				

The percentages of toluidide, (I.), m-xylidide, (II.), and methylanilide, (III.), produced with various acids at 100° C. are given below:—

X	I.	II.	III.	IV.
	Per cent.	Per cent.	Per cent.	Per cent.
H	92·2	95·0	94·6	92·0
CH_3	17·6	31·6	26·2	25·0
C_2H_5	7·2	11·9	3·6	16·0
n-C_3H_7	2·7	3·0	0·9	8·0
n-C_4H_9	4·2	3·4	1·8	8·0
i-C_3H_7	1·4	0·0	0·3	11·0
i-C_4H_9	—	—	—	2·0
$HO.CH_2$	28·4	44·6	20·4	13·0
$HO.CH(CH_3)$	20·4	26·5	11·8	12·0
$HO.CH(C_2H_5)$	14·5	—	4·9	3·0
$HO.CH(C_6H_5)$	14·1	14·7	6·1	0·0
$HO.C(CH_3)_2$	0	1·2	2·4	0·0

The following table[2] shows the affect of the introduction of

[1] Bischoft, *Ber.*, **30**, 2321, 2467, 2475, 2477 (1897).
[2] Bischoff, *ibid.*, **30**, 2774 (1897).

substituents into aniline; *a* represents a propionyl radical, *b* a phenylacetyl radical —

Substituents of aniline.	Ortho-		Meta-		Para-	
	a	*b*	*a*	*b*	*a*	*b*
CH_3	54	43	94	48	92	43
Cl	61	49	87	71	92	72
NO_2	0	42	59	77	5	63

From these two sets of results it appears that hydroxyl radicals exercise a favourable influence; while the phenyl group has a greater hindering effect than methyl; branching of the open chain also tends to hinder the reaction. Bischoff points out that if the Dynamic Hypothesis be applied in this case, it leads to the conclusion that valency may have some connection with steric hindrance; for if we arrange two systems in the usual chain we find—

$$\begin{array}{l} {}^{1}CH_3 \diagdown \\ \quad {}^{2}CH - \overset{3}{CH_2} - \overset{4}{CO} - \overset{5}{O} - NH_3 - C_6H_5 \\ {}^{1}CH_3 \diagup \end{array}$$

(I.) Favourable.

$$\begin{array}{l} {}^{1}CH_3 \diagdown \\ \quad {}^{2}CH - \overset{3}{CH_2} - \overset{4}{CO} - \overset{5}{NH} - C_6H_5 \\ {}^{1}CH_3 \diagup \end{array}$$

(II.) Unfavourable.

In (I.) the oxygen atom stands in the δ-position to the methyl groups, while in (II.) the nitrogen atom is thus placed; and if we adopt the vibration idea of valency, it will be seen that the oxygen atom is liable to collide with two radicals (the CO and NH_3), and thus must move in two directions; while the nitrogen atom in (II.) collides with three (CO, H, and phenyl), and therefore moves in three directions: from which it seems probable that it has more chance of collision with the methyl groups than the oxygen atom has.

Vorlander and Weissbrenner[1] found that when ammonia was allowed to act for one and a half to two hours upon the diethyl ester of phenylglycin-*o*-carboxylic acid, a certain quantity of a monamide was formed along with the diamide, which appeared to point to the fact that there was not enough space to allow the entrance of the second amido-group. The same result was observed when aniline was substituted for ammonia. The most recent work in this branch of the subject is due to Fischer and Dilthey,[2] who studied the action of ammonia upon alkyl-malonic, phenyl-acetic, and benzoic esters. Their results with liquid ammonia at 17° C. are shown in the table below :—

Substance.	Days.	Per cent.
Malonamide	10	63
Methyl-malonamide	28	50
Ethyl-malonamide	21	63
Propyl-malonamide	21	89
Diethyl-malonamide	60	1·1
Dipropyl-malonamide	60	2·6
Phenyl-acetamide	—	23·4
Benzamide	—	5·37

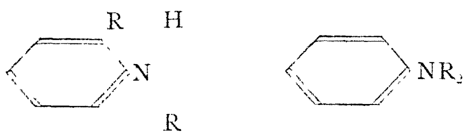
The last two numbers give the amount formed after 26 hours at 125° C., with alcoholic ammonia, saturated at 0° C. :—

Substance.	Time.	Temperature.	Per cent.
Malonamide	5 days	17°	98
Methyl-malonamide	5 ,,	18°	34
,, ,,	26 hours	130°	40
Ethyl-malonamide	26 ,,	130°	53
Propyl-malonamide	26 ,,	130°	61
Dimethyl-malonamide	30 ,,	145°	2·6
Diethyl-malonamide	12 ,,	140°	Trace
Dipropyl-malonamide	12 ,,	150°	0
Phenyl-acetamide	26 ,,	175°	75
Benzamide	26 ,,	175°	16·8

[1] Vorlander and Weissbrenner, *Ber.*, **33**, 556 (1900).

[2] Fischer and Dilthey, *ibid.*, **35**, 4128 (1902).

Space relations appear to affect certain reactions of the aromatic bases, in a few cases to such an extent as to alter the whole chemical character of the substances in question. Instances are to be found in the work of Weinberg,[1] Bernthsen,[2] Rosenstiehl,[3] Busch,[4] Blumer,[5] and Gnehm.[6] For instance, it appears that usually a secondary base has not the property of condensing with an aldehyde to form a derivative of triphenylmethane; but if a methyl group be introduced in the ortho-position, the compound becomes capable of uniting with aldehydes, and in this resembles a tertiary base. In other words, (I.) behaves like (II.).

(I.)  (II.)

Again, in the cases of nitroso-compound formation and coupling with diazo-compounds, somewhat similar phenomena are noticeable. When treated with nitrous acid, a tertiary aromatic amine with no substituent in the para-position to the nitrogen atom is converted into a nitroso-body; but if a methyl group be introduced in the ortho-position to the nitrogen, this faculty is destroyed. Dimethyl-aniline combines with diazo-compounds to produce amido-azo bodies, but here also the introduction of an ortho-substituent has a hindering effect upon the reaction. Friedländer[7] explains these facts by assuming that in all three cases the first step is the formation of an addition compound with the reagent used (aldehyde, nitrous acid, or diazo-compound), and that thereafter an intramolecular change takes place, resulting in the production of a

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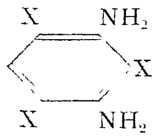
[1] Weinberg, *Ber.*, **25**, 1610 (1892); **26**, 307 (1893).
[2] Bernthsen, *ibid.*, **25**, 3128, 3366 (1892).
[3] Rosenstiehl, *Compt. rend.*, **115**, 180 (1892).
[4] Busch, *Ber.*, **32**, 1008 (1899).
[5] Blumer, *Annalen*, **304**, 87 (1898).
[6] Gnehm, *ibid.*, **304**, 95 (1898).
[7] Friedlander, *Monatsh.*, **19**, 627 (1898).

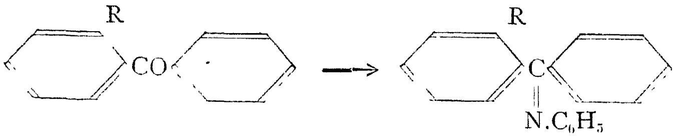
para-substituted compound. The presence of ortho-substituents tends to hinder the formation of the addition compound, and so prevents the reaction taking the usual course.

Morgan[1] found that the successive replacement by methyl of the hydrogen atoms X in *m*-phenylene-diamine :—



decreases the reactivity of the amido-group ; and when all three X atoms are replaced by radicals, methyl bromide or chloride has no action on the compounds.

On the other hand, Graebe[2] has shown that in some cases an ortho-substituent may exercise a favourable influence upon the course of a reaction. He found that the replacement of the ketonic oxygen of benzophenone derivatives by the radical C_6H_5—N: was rendered more easy when one ortho-substituent was present.



Quantitative experiments seemed to show that the chemical nature of the substituent had a considerable influence upon the amount of hindrance caused by it ; so that it is hardly possible to consider the phenomenon as one depending wholly upon stereochemical relations.

Menschutkin[3] showed that in the acetylation of amines the ortho-substituent had a greater hindering effect than meta- and para-substituents. His figures for the toluidines, arrived at for acetylation at 183° C. without a solvent, were :—

[1] Morgan, *Trans.*, **81**, 650 (1902)
[2] Graebe, *Ber.*, **32**, 1678 (1899).
[3] Menschutkin, *J. Russ. Phys. Chem. Soc.*, **32**, 46 (1900)

	Ortho-	Meta-	Para-
30 minutes . .	42·6	58·7	67·5
10 hours	65·7	78·4	81·6

Potozki[1] studied the acetylation of some unsaturated amines, and was able to confirm Menschutkin's conclusion that the velocity of acetylation could be used to determine whether a given amine was primary, secondary, or tertiary. Cybulsky[2] measured the speed of acetylation of certain derivatives of quinoline and naphthalene. His results for a temperature of 210° C. were as follows:—

Substance.	Amount formed in half an hour.
Aniline	68·7
α-Naphthylamine	35·0
β-Naphthylamine	69·1
α-Tetrahydronaphthylamine . . .	63·3
β-Tetrahydronaphthylamine . .	89·7
Tetrahydroquinoline	16·8
Tetrahydro-*o*-toluquinoline . .	1·2
Tetrahydro-*m*-toluquinoline . .	12·5
Tetrahydro-*p*-toluquinoline	20·7

§ VIII. *DECOMPOSITION AND POLYMERISATION.*

When a compound under certain conditions has a tendency to break down in any way, it is usually possible by substituting in it complex radicals for simple ones to facilitate its decomposition. The reason for this appears to be that the substituents take up a certain amount of space, and that in this way the rest of the molecule is more crowded together than it was originally; as decomposition entails the loss of several atoms, it will tend to lessen the crowding effect, and hence the more substituents we introduce the more decomposition ensues, in order that a condition of stability may be reached.

[1] Potozki, *J. Russ. Phys. Chem. Soc.*, **35**, 339 (1903).
[2] Cybulsky, *ibid.*, 219.

A case in point is that of the substituted malonic acids. The reaction takes place as follows:—

$$\begin{array}{c} COOH \\ | \\ X-C-H \\ | \\ COOH \end{array} \quad = \quad CO_2 + \begin{array}{c} COOH \\ | \\ X-C-H \\ | \\ H \end{array}$$

The figures below give the percentage of acid thus decomposed in five minutes where X varies:—

X.	Per cent. decomposed.
$(CH_3)_3.C$-	37·4
CH_3-	39·2
$CH_3.CH_2$-	42·5
H-	42·9
$CH_3.CH_2.CH_2$-	44·9
$CH_2:CH\text{-}CH_2$-	63·4
$C_6H_5\text{-}CH_2$-	69·8

Substituents appear to influence the ease with which hydriodic acid is lost by some alkyl iodides, as the following figures[2] show. They represent the maximal velocity of the reaction between alcoholic potash and the alkyl iodide:—

4.00	$I-C(CH_3)_3$
2.32	$I-\begin{array}{l} CH_3 \\ CH \\ C_2H_5 \end{array}$
1.42	$I-CH_2-CH(CH_3)_2$
1.42	$I-CH(CH_3)_2$
1.00	$I-CH_2-CH_2-CH_3$
0.83	$I-CH_2-CH_3$
0·50	$I-CH_2-CH_2-CH_2-CH_3$

In neither of the last two cases does there seem to be any general conclusion to be drawn from the figures, at least in

[1] Hjelt, *Ber.*, **27**, 1178 (1894).

[2] Brussow, *J. Russ. Phys. Chem. Soc.*, **32**, 7 (1900); *Zeit. physikal. Chem.*, **34**, 129 (1902).

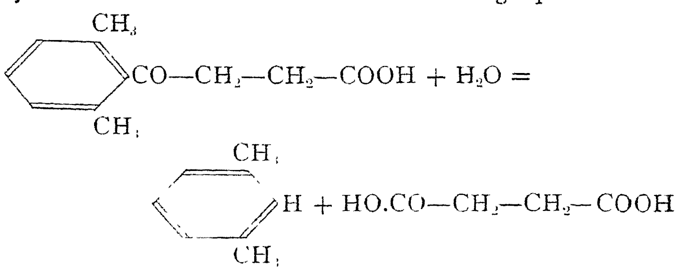
reference to the influence of special groups: they serve merely to indicate that when one group is substituted for another a certain change in the character of the substance takes place, which probably is due to spacial relations.

Several other cases may be described in which substituents assist a decomposition reaction. When certain phenoxy-fatty acids are distilled, they break down according to the following equation:—

$$C_6H_5{-}O{-}\underset{\displaystyle CH_3}{\overset{\displaystyle X}{\overset{|}{\underset{|}{C}}}}{-}COOH = C_6H_5{-}OH + CH_2{:}CX{-}COOH$$

If X be a hydrogen atom, the methyl group can be replaced by ethyl or isopropyl, and the acid will remain stable under distillation; but if X be a methyl group then all three acids will break down as shown in the equation.[1]

Hoogewerff and van Dorp[2] have found that while acetophenone cannot be broken down by sulphuric acid, ortho-mono- and di-substituted acetophenones can be thus decomposed; and Muhr[3] has observed a similar instance in derivatives of carboxylic acids. He found that though benzoylpropionic acid was stable in the presence of hydriodic or hydrochloric acid, its di-ortho-dimethyl derivative was decomposed by heating with hydriodic acid in accordance with the following equation:—



[1] Bischoff, *Ber.*, **33**, 928 (1900).

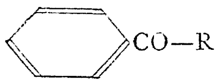
[2] Hoogewerff and van Dorp, *Proc. K. Akad. Wetensch.* Amsterdam, **1901**, 173.

[3] Muhr, *Ber.*, **28**, 3215 (1895).

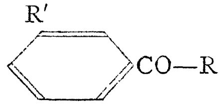
Klages and Lickroth[1] have examined the behaviour of their phosphoric esters of ketones * when heated; and have found that substituents have a great effect upon the stability of the compounds. Their method was simply to boil the ketone with phosphoric acid, producing the corresponding hydrocarbon and fatty acid, no isolation of the intermediate ester being attempted in this case.

$$R—CO—CH_3 + H_2O = R.H + HO.CO.CH_3$$

(I.)



(II.)



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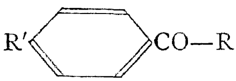

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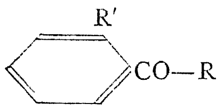

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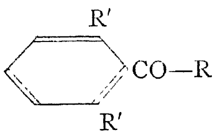

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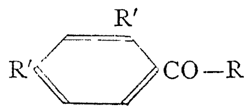
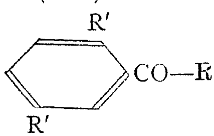
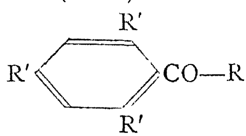


(VII.)



(VIII.)



In the compounds of type (I.), R was a methyl, propyl, or butyl radical; in (II.) R and R′ were both methyl; in (III.) R was propyl and R′ was ethyl. No decomposition took place

* See *ante*, p. 406.

[1] Klages and Lickroth, *Ber.*, **32**, 1549 (1899).

in any of these cases. The types (IV.) and (VI.) were decomposed, losing their parent hydrocarbons, in eight hours to the extent of 20 to 30 per cent.; (V.), in the same time, was completely decomposed. The influence of a greater number of substituents is practically nil, and no difference is noticed when isopropyl is substituted for methyl in R of (VII.). In (VIII.), if R be benzyl, and there be no substituents in the place of R′, no decomposition occurs: when three methyls are introduced instead of the R′ radicals, decomposition takes place.

Menschutkin, Kriger, and Ditrich[1] studied the decomposition of various organic salts of dimethylamine when heated to 212°:—

$$R.CO.ONH_2(CH_3)_2 = R.CO.N(CH_3)_2 + H_2O$$

The following figures give the amount of decomposition during the first hour:—

Acid.	Amount.
Acetic	84·79
Propionic	81·59
n-Butyric	76·11
i-Butyric	48·57
Benzoic	23·26
o-Toluic	19·42
m-Toluic	26·44
p-Toluic	24·89
Mesitylenic	29·34
Phenyl-acetic	75·61
Phenyl propionic	71·44

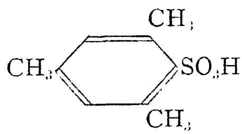
From these, and also from his previous researches[2] on the same subject, Menschutkin draws the following conclusions. The rate of amide formation is greatest with normal fatty acids; forking of the chain decreases it more or less according as the carboxyl group is near to or removed from the fork. In aromatic or tertiary fatty acids the rate of formation is low;

[1] Menschutkin, Kriger, and Ditrich, *J. Russ. Phys. Chem. Soc.*, **35**, 103 (1903).
[2] Menschutkin, *ibid.*, **26**, 61 (1894); *Ber.*, **31**, 1423 (1898).

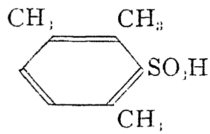
side chains in the ortho-position lower the rate, while those in the meta- and para-positions may accelerate it. Aromatic acids in which the carboxyl group is attached to the side chain are analogous to fatty acids; they show great reaction velocity in normal chains, but a decrease when the chain branches.

Crafts[1] has found that methyl groups exercise a considerable influence upon the decomposition of the sulphonic acids of mesitylene and pseudocumol:—

(I.)



(II.)



When treated with 38 per cent. hydrochloric acid at 80° C., (I.) is hydrolysed in fifteen minutes, sulphuric acid being liberated, while (II.), even after five hours, shows no signs of decomposition.

Very few facts are known which throw light upon the relation of steric influences to the phenomenon of polymerisation. The influence of substituted methyl groups is shown in the case of the polymerisations of acids belonging to the acrylic series. Acrylic and α-methyl-acrylic acids can be polymerised, but β-methyl-acrylic acid cannot. Auwers,[2] in the course of his cryoscopic researches, has shown that the faculty possessed by phenols of forming complex molecules in solution is much influenced by substitution in the ortho-position.

§ IX. *CONCLUSION.*

In the preceding sections of this chapter a detailed account has been given of the most important researches on the phenomena of steric hindrance, and at this point it seems

[1] Crafts, *Ber.*, **34**, 1360 (1901).

[2] Auwers, *Zeit. physikal. Chem.*, **18**, 621 (1895); **21**, 337 (1896); *Ber.*, **31**, 3039 (1898).

desirable to summarise the results to which these researches have led us. For the sake of convenience the conclusions may be classified under the same heads as were used in the case of the experimental work.

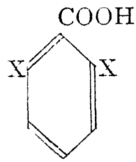
Esterification.—The velocity with which any ester is formed depends upon several factors, the chief ones being (1) the method of esterification, (2) the structure of the given acid, and (3) the structure of the given alcohol. As regards the first factor, it is found that spacial influences appear to play no noticeable part in ionic reactions; but when the reaction is non-ionic (as in the case of esterification with alcohol and hydrochloric acid), space relations exert a greater influence upon the course of the reaction. In the case of alcohols, it has been observed that when the same acid is esterified with three isomeric alcohols (normal, secondary, and tertiary), the amounts of ester formed under identical conditions differ considerably in the three cases, the normal alcohol yielding most, the tertiary one least, ester. This is attributed to the accumulation of substituents round the hydroxyl group in the cases of the secondary and tertiary alcohols. A similar phenomenon is observed in the case of a normal and an isomeric iso-acid when they are esterified with the same alcohol, the iso-acid yielding less ester than the normal one under the same conditions. In the case of unsaturated stereoisomeric acids, the spacial position of the substituents appears to exercise a marked influence on the ease of esterification. The following formulæ give an idea of the results obtained :—

$$\begin{array}{ll}
\begin{array}{c}\mathrm{Y{-}C{-}H}\\ \|\\ \mathrm{X{-}C{-}COOH}\end{array} & \begin{array}{c}\mathrm{H{-}C{-}Y}\\ \|\\ \mathrm{X{-}C{-}COOH}\end{array}\\
\text{Easily esterified.} & \text{Hard to esterify.}\\[1em]
\begin{array}{c}\mathrm{Y{-}C{-}Z}\\ \|\\ \mathrm{X{-}C{-}COOH}\end{array} & \begin{array}{c}\mathrm{Y{-}C{-}Z}\\ \|\\ \mathrm{H{-}C{-}COOH}\end{array}\\
\text{Very hard to esterify} & \text{Easily esterified.}
\end{array}$$

Saturated acids are much more easily esterified than the corresponding unsaturated ones; *e.g.* butyric acid is easier to esterify

than crotonic acid. The influence of substituents is not confined to mono-basic fatty acids, but is shown also in the poly-basic fatty and alicyclic series.

Turning now to the aromatic acids, we find a similar series of phenomena. Benzoic acid is easily esterified; but di-substituted benzoic acids of the type:—



where X represents an alkyl radical, nitro-group, or halogen atom, are hard to esterify. It seems to be proved that the reaction is influenced by the size or weight of X rather than by its chemical character. Similar results have been obtained in the case of aromatic di- and poly-basic acids.

From the results now available, it seems clear that esterification by means of hydrochloric acid and alcohol takes place in two stages:—

(I.)

$$R\!-\!\overset{\displaystyle O}{\overset{\|}{C}}\!-\!OH + EtOH = R\!-\!\underset{\displaystyle OH}{\overset{\displaystyle OEt}{C}}\!-\!OH$$

(II.)

$$R\!-\!\underset{\displaystyle OH}{\overset{\displaystyle OEt}{C}}\!-\!OH = R\!-\!\overset{\displaystyle OEt}{C}\!=\!O + H_2O$$

The compound formed it Stage (I.) contains the large group:—

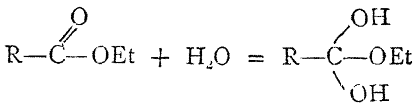
$$-\underset{\displaystyle OH}{\overset{\displaystyle OEt}{C}}\!-\!OH$$

and if the substituents in the radical R be sufficiently bulky to

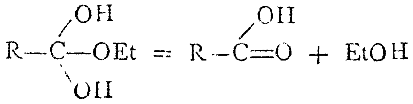
occupy so much space as to prevent the entry of an alcohol molecule, this intermediate product will not be easily formed, and the yield of the ester will consequently be small.

Hydrolysis.—This reaction also is supposed to require the formation of an intermediate compound, which in the case of ester hydrolysis would be represented thus:—

(I.)



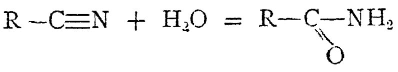
(II.)



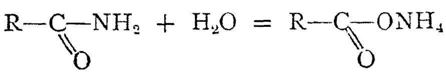
The same influences come into play here as in the case of esterification; hence we find that the ester of a simple acid is more easily hydrolysed than that of a substituted acid. This holds good in both the aliphatic and the aromatic series.

The hydrolysis of a nitrile also takes place in two stages:—

(I.)



(II.)



Substituents in the group R will therefore exercise an analogous effect in this case, and also in the hydrolysis of amides to ammonium salts (Stage (II.) above).

Chain Formation. — When two substances by reacting together form an open-chain compound, the yield of the latter body will depend very largely upon the structure of the two original compounds. It has been shown that if, in the final

product, many substituents lie in the 1,5- or 1,6-positions with regard to each other, a very poor yield must be expected. The formulæ below illustrate the matter graphically :—

(I.) Good yield—

$$\mathrm{R.CH_2.CH_2.CH_2.X \quad X.CH_2.CH_2.CH_2.R} \xrightarrow{-2X}$$

$$\mathrm{\overset{1}{R}.\overset{2}{C}H_2.\overset{3}{C}H_2.\overset{4}{C}H_2.\overset{5}{C}H_2.\overset{6}{C}H_2.CH_2.R}$$

(II.) Good yield—

$$\mathrm{R.CH_2.X \quad X.CH_2.R} \xrightarrow{-2X} \mathrm{\overset{1}{R}.\overset{2}{C}H_2.\overset{3}{C}H_2.\overset{4}{R}}$$

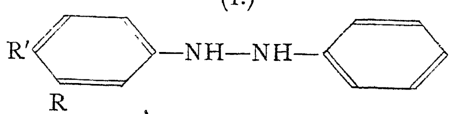
(III.) Bad yield—

$$\mathrm{R.CH_2.CH_2.X \quad X.CH_2.CH_2.R} \xrightarrow{-2X} \mathrm{\overset{1}{R}.\overset{2}{C}H_2.\overset{3}{C}H_2.\overset{4}{C}H_2.\overset{5}{C}H_2.\overset{6}{R}}$$

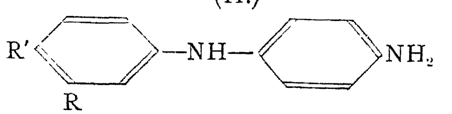
As was mentioned in Section I. of this chapter, if any reaction can give rise to two series of products, those products will predominate in which there are fewest atoms in the 1,5- or 1,6-positions.

Intramolecular Change.—If any compound be capable of intra-molecular rearrangement into either of two other compounds, the compound formed in greatest quantity will be that *in which the substituents are most evenly distributed in the molecule.* For instance, the compound (I.) is theoretically capable of yielding either (II.) or (III.). In practice, however, owing probably to the space occupied by the substituents, (II.) is always formed, as in it they have more free play than they have in (III).

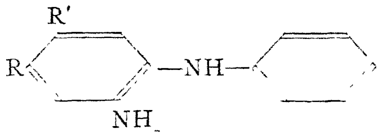
(I.)



(II.)



(III.)



Addition.—When new atoms are introduced into a molecule, the ease with which they enter depends to some extent upon the amount of space available within the molecule. By replacing small groups of atoms by larger radicals, addition reactions may thus be hindered. It should be noted, however, that in some cases a compound (say XYZ) may only be formed with great difficulty from two of its possible constituents (say X and YZ), while if two other constituents (Y and ZX) be utilized, its formation may be quite easy.

Substitution.—Since probably most substitution reactions are carried out in two stages, the first of which is an addition reaction, it is to be expected that spacial influences will affect substitution reactions, just as they modify addition reactions. Such effects have been observed in the cases of many reactions, *e.g.* acetylation, oximation, anilide formation, and the action of ammonia upon esters.

Decomposition.—If a compound be easily decomposed, its homologues are often found to be more unstable than the parent substance. The reason for this must be sought in spacial relations. In the parent substance, we may suppose that the atoms are "crowded together" and have not sufficient free space for their vibrations. If this free space be still further diminished by the introduction of more atoms, it is obvious that the "crowding" may become so great as to force a decomposition.

CHAPTER II.

THE RELATION BETWEEN SPACE FORMULA AND CHEMICAL PROPERTIES.

In considering the question of the stability of cyclic compounds, there are two ways in which the problem may be approached: for the stability of a ring compound may be deduced either from the ease with which the ring can be opened; or from the difficulty found in closing an open-chain compound to a ring.

In the latter case, it is found that there are three points which appear most important: they are (1) the number of atoms in the open chain, (2) the positions in space occupied by the atoms which are directly concerned in the closing of the ring, and (3) the nature of the atoms which are attached to the atoms of the chain which do not take part in the ring-formation.

As regards the first point, it appears from the results now at our disposal that five or six carbon atoms in a chain lend themselves to ring-formation better than a greater or less number. Instances of the second point have already been mentioned in the preceding pages: *e.g.* the formation of maleic anhydride from maleic acid is easier than from fumaric acid, because the hydroxyl groups lie nearer together in space in maleic than they do in fumaric acid. Examples of the third point will be dealt with in the last chapter of this book.

§ I.—*BAEYER'S STRAIN THEORY.*

The formation of closed carbon chains is probably the most certain means at present at our disposal for the investigation

of the space positions and relations of carbon atoms; for it must be supposed that two carbon atoms will be linked together easily if they normally lie near to one another in space, while great difficulty will be found if they have to be strained into position in order that a ring may be formed. From this starting-point, Baeyer[1] deduced his *Strain Theory*, which may be formulated as follows:—

"*The four valencies of a carbon atom act parallel to lines joining the corners of a tetrahedron with its centre, making an angle of* 109° 28′ *with one another. The direction of the valencies can be altered, but any such alteration produces a strain whose amount is proportional to the angle through which the valencies are diverted.*"

The application of this idea to the various ring compounds is simple. Taking the case of trimethylene, it is assumed that the three carbon atoms are symmetrically placed with regard

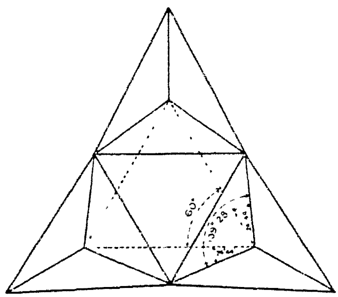


FIG. 45.

to one another; that is to say, they lie at the angles of an equilateral triangle. The valencies joining them must therefore be inclined to one another at an angle of 60°. But normally these valencies are supposed to lie at an angle of 109° 28′ to one another; so that each of them must have been diverted through an angle of $\frac{1}{2}$ (109° 28′ − 60°) = + 24° 44′.

[1] Baeyer, *Ber.*, **18**, 2277 (1885).

A general formula, giving the deviation for a ring-compound containing any number of carbon atoms, is :—

$$\tfrac{1}{2}\left[109^\circ\ 28' - \frac{2(n-2)}{n} \cdot 90^\circ\right]$$

where n is the number of atoms in the ring.

Calculated thus, the figures for the known polymethylenes are :—

	Angle of deviation.
(Ethylene)	54° 44′
Trimethylene	24° 44′
Tetramethylene	9° 44′
Pentamethylene	0° 44′
Hexamethylene	−5° 16′
Heptamethylene	−9° 33′
Octomethylene	−12° 51′

The theory assumes that all the carbon atoms lie in the same plane, as otherwise the strain would not be calculable in the way given. The conclusions to be drawn from the above figures are obvious. If they be correct, then pentamethylene must be the most stable of all the saturated rings, while tetramethylene and heptamethylene should be of approximately the same stability. Some proof of the general correctness of the results can be found in the heats of combustion of some of the polymethylenes. For example, the following numbers[1] represent the energy required in each case to break the ring and add on two hydrogen atoms :—

Trimethylene	38·1 cal.
Tetramethylene	42·6 cal.
Pentamethylene	16·1 cal.
Hexamethylene	13·9 to 14·8 cal.

Traube,[2] from a consideration of atomic volumes in cyclic

[1] Stohmann and Kleber, *J. pr. Chem.*, [2] **45**, 475 (1892), compare Meyer and Jacobson, *Lehrbuch der organischen Chemie*, II., **1**, 7.

[2] Traube, *Ueber den Raum der Atome* (*Ahrens Vortragssammlung*, IV.).

compounds, has given further support to the probability of the Strain Theory being correct.

There are, however, several cases known in which reactions do not seem to follow the course which would be expected if Baeyer's idea really represented the actual state of things in the molecule. Perkin,[1] junior, pointed out that while the figures for the compounds with a positive angle of deviation agreed fairly well with what we know of the properties of these substances, this was not true to the same extent for hexamethylene, heptamethylene, and octomethylene, which have negative deviations. There are also difficulties in the case of the relative stabilities of pentamethylene and hexamethylene, as these compounds can be converted into one another; instances of this will be given later. Cases are known, also, in which a trimethylene compound is produced by a reaction which should apparently lead to a hexamethylene derivative. Thus Perkin[2] junior, by the action of dibromopropane-tetracarboxylic ester upon the disodium salt of propane-tetracarboxylic ester, expected to produce hexamethylene-octocarboxylic ester, (I.), but the product actually formed was trimethylene-tetracarboxylic ester. (II.) :—

$$\text{(I.)}\qquad \begin{array}{c} (EtOOC)_2C—CH_2—C(COOEt)_2 \\ \quad\;\;|\qquad\quad\;\;| \\ (EtOOC)_2C—CH_2—C(COOEt)_2 \end{array}$$

$$\text{(II.)}\qquad \begin{array}{c} CH_2 \\ (EtOOC)_2C——C(COOEt)_2 \end{array}$$

§ II. *THE RELATIVE STABILITY OF THE SATURATED CYCLIC COMPOUNDS.*

Trimethylene.—This is the most unstable of all the polymethylenes. The ring may be opened by acting upon it with hydrochloric, hydrobromic, hydriodic, or sulphuric

[1] Perkin junior, *Ber.*, **35**, 2105 (1902).
[2] Perkin junior, *Trans.*, **87**, 358 (1905).

acids.[1] It is not attacked by permanganate, in which it differs from propylene.[1] Bromine acts very slowly upon trimethylene,[2] so that the cyclic compound does not appear to be so unsaturated as the isomeric olefine; but a different conclusion must be drawn from the results of Berthelot's work[3] on the heats of formation of trimethylene and propylene derivatives.

	Heat of formation.	Bromine addition	Sulphuric acid addition.
Trimethylene	−17·1 cal.	+38·5 cal.	+25·5 cal.
Propylene	−9·4 cal.	+29·1 cal.	+16·7 cal.

The differences shown in the table above indicate that trimethylene has an energy content about eight calories greater than that of propylene.

Tetramethylene.—The root-substance of this series is as yet unknown. It appears to be unstable; but this instability has apparently little connection with the strain produced in the ring, for many other four-membered carbon rings are known. Methyl-tetramethylene, which is the lowest member of the tetramethylenes synthesised up to the present, is more stable than the corresponding trimethylene derivative, as it resists the action of cold hydriodic acid. A further example of this difference might be mentioned: acetyl-tetramethylene can be reduced to a secondary alcohol without breaking the ring; but when acetyl-trimethylene is reduced, the ring opens, and an open-chain amyl alcohol is formed. Tetramethylene-mono-carboxylic acid is comparatively stable to hydrobromic acid, under conditions which convert trimethylene-mono-carboxylic acid into γ-bromo-butyric acid. Tetramethylene derivatives can sometimes be converted into those of the pentamethylene series by suitable reagents. For instance, Demjanow[4] has shown that

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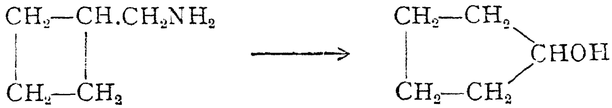
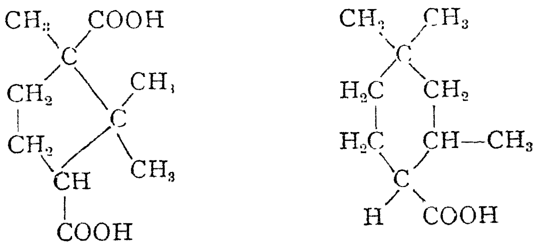
[1] Freund, *Monatsh.*, **3**, 626 (1882).
[2] Wagner, *Ber.*, **21**, 1236 (1888).
[3] Berthelot, *Compt. rend.*, **129**, 483 (1899).
[4] Demjanow, *J. Russ. Phys. Chem. Soc.*, **35**, 26 (1903).

when cyclobutyl-methylamine is treated with nitrous acid it gives rise, in addition to the normal product, to a small quantity of a pentamethylene derivative :—



Pentamethylene.—The root substance is not attacked by boiling with hydriodic acid; the mono-carboxylic acid is unattacked after long boiling with hydrobromic acid,[1] and, in general, it may be said that the pentamethylene type is the most stable of all the cyclo-paraffins. On the other hand, there are certain reactions which will be dealt with below, from which it would seem that the hexamethylene and pentamethylene types are almost equally stable.

Hexamethylene.—When camphoric anhydride is treated with aluminium chloride, one of the products is hexahydroxylylic acid.[2] This is an example of the conversion of a five-membered into a six-membered ring :—



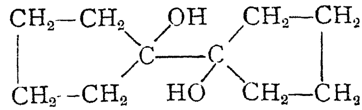
Meister[3] has found a similar instance in a dicyclic compound, for when the pinacone (I.) is treated with dilute sulphuric acid, it is converted into the pinacoline (II.) :—

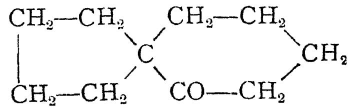
---

[1] Perkin, junior, *Ber*, **35**, 2105 (1902).

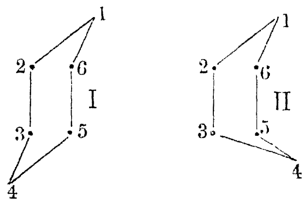
[2] Perkin and Yates, *Trans.*, **79**, 1373 (1900)

[3] Meister, *Ber.*, **32**, 2054 (1899).

(I.) 

(II.) 

On the other hand, Zelinsky[1] and Aschan[2] have shown that some hexamethylene compounds can be rearranged to form pentamethylene derivatives. Hexahydro-iodo-phenol, when heated to 230° C. with hydriodic acid, yields methyl-pentamethylene; and 1-methyl-3-hydroxyhexahydrobenzene, when similarly treated, appears to form dimethyl-pentamethylene. These phenomena are apparently at variance with Baeyer's Strain Theory, but the incongruity may be avoided if certain reservations be made as to the space formula of hexamethylene. If we suppose that the carbon atoms in hexamethylene lie in two planes, it will be found possible to construct two formulæ,[3] in neither of which is there any considerable strain :—



The positions of the carbon atoms may be seen from the following photographs.* In the first case (Fig. 46), the carbon atoms 1,3,5 lie in one plane, while 2,4,6 lie in a parallel one; in the second formula (Fig. 47), the atoms 2,3,5 and 6 lie in a plane, while the line joining 1 and 4 is parallel to that plane.

* Directions for making Sachse's models are given in Appendix B.

[1] Zelinsky, *Ber.*, **29**, 731 (1896); **30**, 1537 (1897).

[2] Aschan, *Annalen*, **324**, 8 (1903).

[3] Sachse, *Ber.*, **23**, 1363 (1890); *Zeit. physikal. Chem.*, **10**, 203 (1892)

These formulæ, however, while freeing us from certain difficulties, involve us in others not less serious. For instance,

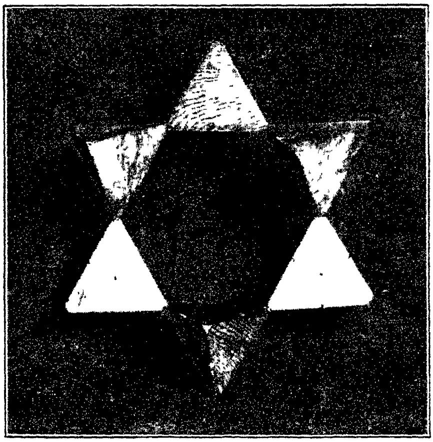


FIG. 46

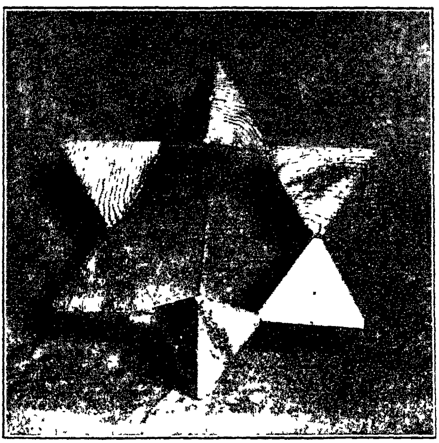


FIG. 47.

in the case of the first formula, since there are two sets of hydrogen atoms there should be two mono-substitution products; further, all disubstitution products ought to occur in optically active forms; but this does not appear to be the case, as Werner and Conrad[1] made the attempt without success in the case of cis-hexahydro-phthalic acid. It would, therefore, seem that the plane formula for hexamethylene is better than Sachse's one. In the second case, the cis-form disubstitution products would give a molecular asymmetry akin to that of inosite. It appears, therefore, that neither of the Sachse models is supported by facts. The two forms may, however, be considered as phases in the vibration of the hexamethylene system; and this assumption frees us from most of the difficulties encountered when each formula is supposed to be a rigid object.

Heptamethylene.—Just as the hexamethylene ring can be converted into the pentamethylene, so can heptamethylene be changed into a six-membered ring,[2] being converted by heating with hydriodic acid into methyl-hexamethylene. An example of the conversion of a hexamethylene into a heptamethylene compound was given by Demjanow,[3] who showed that when silver nitrite acts on cyclohexyl-methylamine hydrochloride, suberyl alcohol is formed:—

$$\begin{array}{l} CH_2-CH_2-CH_2 \\ | \qquad\qquad\quad | \\ CH_2-CH_2-CH-CH_2NH_2 \end{array} \longrightarrow \begin{array}{l} CH_2-CH_2-CH_2 \\ | \qquad\qquad\qquad\quad \diagdown \\ | \qquad\qquad\qquad\qquad CHOH \\ | \qquad\qquad\qquad\quad \diagup \\ CH_2-CH_2-CH_2 \end{array}$$

Octomethylene.—Nothing definite is known as to the stability of this series; the compounds are certainly less stable than hexamethylene or heptamethylene.

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[1] Werner and Conrad, *Ber.*, **32**, 3046 (1899).
[2] Markownikow, *J. Russ. Phys. Chem. Soc.*, **25**, 547 (1893).
[3] Demjanow, *ibid.*, **36**, 166 (1904).

§ III. *THE INFLUENCE OF THE POSITION OF ATOMS IN SPACE ON THEIR ABILITY TO FORM RINGS.*

1. In Carbocyclic Compounds.—From his assumption of the tetrahedral form of the carbon atom, van't Hoff deduced that the distance between two atoms in an open-chain carbon compound will not increase indefinitely, as the chain is lengthened by the addition of new atoms. Instead of this, the chain will tend to curve round, and its ends will approach nearer and nearer to each other, until there are five atoms in the chain, after which the ends will cease to approach each other, as new atoms are

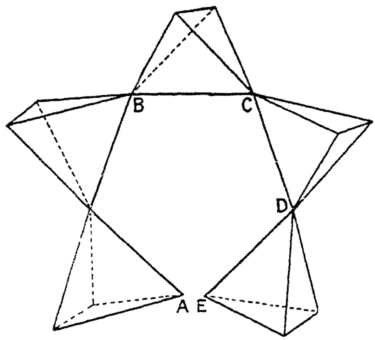


FIG. 48.

added. Fig. 48 illustrates this view. It has been calculated by van't Hoff that the distances AB, AC, AD, and AE stand to one another in the ratios 1 : 1·02 : 0·67 : 0·07. So that on this theory the valency centres of atoms at the ends of a five-membered chain would be much nearer together than the valency centres of the end atoms of any chain of less than five atoms; and a five-membered ring would therefore be more stable than one with a greater or less number of atoms in it.

Almost without exception, this idea has been supported by the investigations which have been made upon this subject. It is, therefore, unnecessary to quote instances of the results obtained, the more so since a complete account of the matter

will be given in Chapter VI. There are, however, a few cases in which the reaction does not follow the lines which might be expected from the theory. One or two of these may be mentioned.

(1). Trimethylene bromide reacts with zinc to form trimethylene, and not, as might have been expected, hexamethylene.[1]

(2). Acetyl-propyl-bromide, on treatment with solid potash, gives acetyl-trimethylene, and not a hexamethylene derivative.[2]

(3). α-Brom-glutaric ester, when treated with potash or quinoline, gives trimethylene-dicarboxylic acid :—[3]

$$CH_2\begin{array}{l} \diagup CH_2—COOEt \\ \\ \diagdown CHBr.COOEt \end{array} = HBr + CH_2\begin{array}{l} \diagup CH—COOEt \\ \quad | \\ \diagdown CH—COOEt \end{array}$$

(4). Carbonic acid is formed in an exactly similar way when dimethyl-bromoglutaric ester is treated with alcoholic potash.[4]

2. In Heterocyclic Compounds.—In the case of those rings which contain atoms other than carbon, the Strain Theory is not intended to be applied; but, nevertheless, in many cases results have been obtained which point to the same conclusions as those arrived at in the case of the carbocyclic series. For instance, diacetylacetone, which is an open-chain substance, loses water merely by standing at ordinary temperatures, and is converted into the more stable ring compound, dimethylpyrone :—

$$CH_3.CO.CH_2.CO.CH_2.CO.CH_3 \longrightarrow CO\begin{array}{l} \diagup CH:C—CH_3 \diagdown \\ \qquad\qquad\quad O \\ \diagdown CH:C—CH_3 \diagup \end{array} + H_2O$$

[1] Gustavson, *J. pr. Chem.*, [2] **59**, 302 (1899).

[2] Lipp, *Ber.*, **22**, 1207 (1889); Idzowska and Wagner, *J. Russ. Phys. Chem. Soc.*, **30**, 259 (1898).

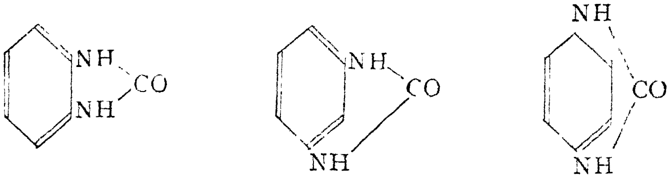
[3] Bowtell and Perkin junior, *Proc.*, **15**, 241 (1899).

[4] Perkin junior and Thorpe, *Trans.*, **75**, 50 (1899).

This is probably due to the close proximity of the two carbon atoms, to which the bridge oxygen atom is attached.

Miolati[1] has shown that the velocity with which the ring of glutarimide opens is about a hundred times greater than is the case with succinimide, so that the ring composed of one nitrogen and four carbon atoms is much more stable than one made up of a nitrogen and five carbon atoms.

R. Meyer[2] states that when the three following compounds are heated with concentrated hydrochloric acid, only the first remains stable.



A hydroxy-acid, containing as it does both a hydroxyl and a carboxyl group in its molecule, might be expected to lose a molecule of water and be converted into a lactone. Hjelt[3] was the first to suggest that the arrangement of atoms in space was the cause of certain lactones being more easily formed than others, and afterwards, Wislicenus treated the matter very fully from the theoretical point of view in his work, *Die Raumliche Anordnung der Atome.* The facts known at present may be summarised as follows.

α-Hydroxycarboxylic acids do not form compounds by intramolecular loss of water, but instead two molecules unite :—

$$\begin{array}{l} CH_3\text{—}CH\text{—}OH \\ \qquad\quad | \\ \qquad\; CO\text{—}OH \end{array} \quad \text{does not give} \quad \begin{array}{l} CH_3\text{—}CH \\ \qquad\;\; | \;\;\; \diagdown \\ \qquad\;\; \;\;\;\; O \\ \qquad\; CO \diagup \end{array}$$

but two molecules give

$$\begin{array}{l} CH_3\text{—}CH\text{—}O\text{—}CO \\ \qquad\quad |\qquad\qquad | \\ \qquad\; CO\text{—}O\text{—}CH\text{—}CH_3 \end{array}$$

---

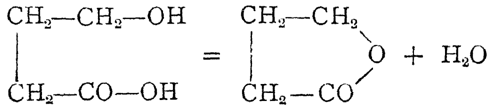
[1] Miolati, *Atti R. Accad. Lincei*, **3**, 515 (1894)

[2] R. Meyer, *Naturwiss Rundschau*, **16**, 477, 494 (1901)

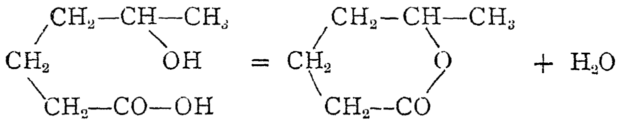
[3] Hjelt, *Ber.*, **15**, 630 (1882).

β-Hydroxycarboxylic acids usually form unsaturated acids, and do not condense to cyclic compounds.

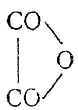
γ-Hydroxycarboxylic acids probably form lactones more easily than any of the other classes; the breakdown often takes place spontaneously:—



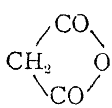
δ-Hydroxycarboxylic acids also easily form lactones, though not with the same readiness as is found in the γ-acids:—



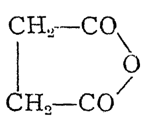
If the series of dicarboxylic acids be considered, beginning with oxalic acid, it will be found that neither oxalic nor malonic acid yields an anhydride; succinic acid can be made to lose water by simple heating; glutaric anhydride is rather more difficult to prepare; while adipic and the higher homologues require special methods, such as heating the acid with acetyl chloride. On writing the formulæ of the hypothetical and actual anhydrides, it will be seen that three- and four-membered rings are not formed, while five- and six-membered ones appear to be most easily formed. The names of non-existent anhydrides are printed in italics:—



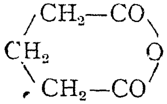
Oxalic.



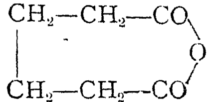
Malonic.



Succinic.



Glutaric.



Adipic.

Holleman and Voerman[1] studied the stability of the anhydrides of various dibasic acids in presence of water; but in most cases the results were unsatisfactory, owing to the insolubility of the anhydrides in water. The authors succeeded in making accurate measurements in the cases of succinic and glutaric anhydrides, the former containing a five-membered ring, being more stable than the six-membered ring of the latter. The figures giving the relative reaction velocities of the two compounds in presence of water at 25° C. are:—

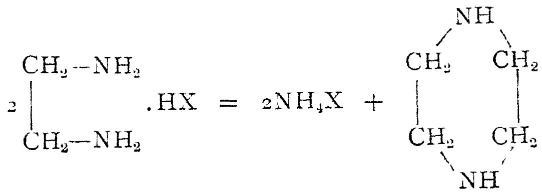
	K
Succinic anhydride	0·1683
Glutaric ,, ...	0·1708

When the salts of primary amines are heated, they are in many cases converted into a mixture of a secondary amine and an ammonium salt:—

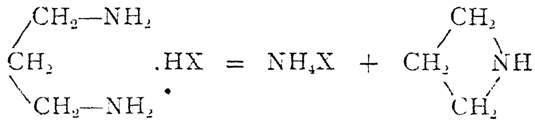
$$2NH_2R.HX = NH_4X + NHR_2.HX$$

And when the same reaction is carried out with a diamido-compound, a cyclic amido-body is formed. If we consider the result of heating the hydrochlorides of various diamido-compounds, we find the following.

Ethylene-diamine does not form a three-membered ring, but instead two molecules condense to form piperazine:—



Trimethylene-diamine produces a mixture of β-methyl pyridine and trimethylene imide:—



[1] Holleman and Voermann, *Proc. K. Akad. Wetensch.* Amsterdam, **1903**, 589.

Tetramethylene-diamine and pentamethylene-diamine condense intramolecularly to form respectively pyrrolidine and piperidine.

Another series of experiments also shows the influence of the number of atoms in the chain. Bischoff[1] condensed formaldehyde with various diamido-compounds, and came to the following conclusions. Compounds of the type $X\text{–}\underset{\cdot}{N}\text{–}\underset{\cdot}{N}\text{–}X$ condensed easily with formaldehyde, but formed six-membered rings. The same is the case with the type $X\text{–}\underset{\cdot}{N}\text{–}CH_2\text{–}\underset{\cdot}{N}\text{–}X$. A five-membered ring was obtained from the type :—

$$X\text{–}\underset{|}{N}\text{–}CH_2\text{–}CH_2\text{–}\underset{|}{N}\text{–}X.$$

No ring could be formed from bodies of the type $X\text{–}\underset{|}{N}\text{–}CH_2\text{–}CH_2\text{–}CH_2\text{–}\underset{|}{N}\text{–}X$.

§ IV. *CONCLUSION.*

From the instances quoted in the foregoing sections, it seems a clear deduction that the Strain Theory is of fairly general application, though in certain cases the results found in practice are not in agreement with the theory. In the carbocyclic compounds the stability of the ring increases with the number of members until the ring contains five carbon atoms; five- and six-membered rings appear to be of very nearly equal stability; while beyond that the stability of the ring tends to decrease inversely as the number of carbon atoms in it. A ring of eight carbon atoms appears to be the largest which it is possible to synthesise. Similar phenomena are observed in the heterocyclic rings.

[1] Bischoff, *Ber.*, **31**, 3248 (1898).

CHAPTER III.

THE EFFECTS OF SUBSTITUTION UPON THE FORMATION AND STABILITY OF CYCLIC COMPOUNDS.

THE effect of replacing one group in a certain compound by another may be twofold; in the first place, if the chemical nature of the two groups differs to a considerable extent, changes in the character of the whole compound may be brought about; while even if the substituent be similar to the group it replaces, it may occupy a certain amount of extra space and thus hinder the progress of some reaction upon which the original group had no effect. With the first of these influences there is no need to deal here in detail, but in several instances it is so difficult to distinguish between a merely chemical influence and a stereochemical one, that some facts in these pages may appear to be explicable on either supposition.

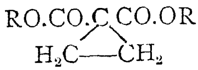
When the stereochemical effects of substitution are considered, it is found that they may be classed in two divisions: first, those cases in which the substitution tends to hinder the course of a certain reaction, and, second, those in which the introduction of new groups facilitates the course of a reaction. The simplest case which can be considered is that of the conversion of an open-chain compound into a ring, and many instances are known in which stereochemical causes prevent such a reaction taking place.

Ipatjew[1] made a series of attempts to synthesise trimethylene rings from the disodium derivative of malonic ester and alkyl dibromides, in the course of which he discovered the following facts. With dibromides whose bromine atoms are

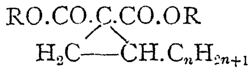
[1] Ipatjew, *J. Russ. Phys. Chem. Soc.*, **30**, 391 (1898); **34**, 351 (1902).

attached to neighbouring carbon atoms, the trimethylene ring was formed only when (1) both bromine atoms are attached to primary carbon atoms, (I.), or (2) one to a primary and the other to a secondary carbon atom, (II.) :—

(I.)

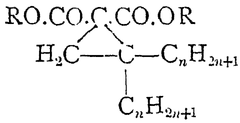


(II.)

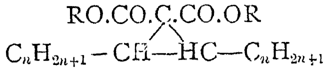


If one bromine atom be attached to a primary carbon, and the other to a tertiary one, no ring is formed, and the same is found if both are attached to secondary carbon atoms. That is to say, the two rings (III.) and (IV.) are not formed :—

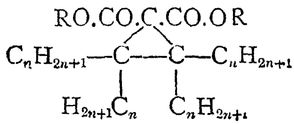
(III.)



(IV.)



And if the bromine atoms are attached to tertiary carbon atoms, no ring-formation takes place :—

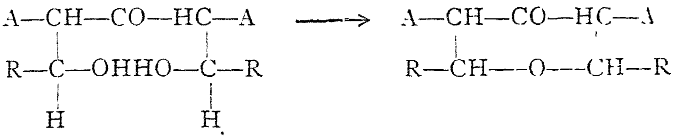


(Not formed.)

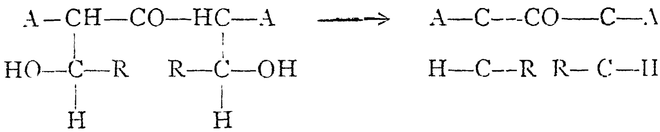
A somewhat similar case is that observed by Petrenko-Kritschenko[1] in the hydropyrones. He found that the formation of the ring in this case depended upon the mutual influence of the groups A and R, attraction leading to configuration (I.) and repulsion to (II.). From (I.) rings are formed, whereas from (II.) only unsaturated ketones are produced

[1] Petrenko-Kritschenko, *Ber.*, 31, 1508 (1898).

(I.)



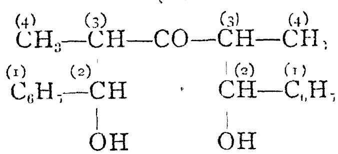
(II.)



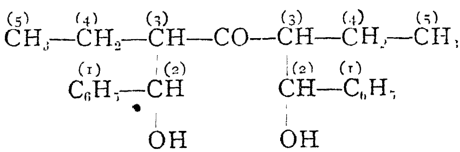
When R was *p*-methoxyphenyl, Petrenko-Kritschenko found that a ring was formed, but when disubstituted phenyls were used, no closing took place.

Vorlander[1] found that though benzaldehyde could easily be condensed with di-ethyl ketone to form a hydropyrone derivative, the same was not possible when di-propyl ketone was used. Bischoff explains this by his Dynamic Hypothesis, since if the compound (II.) were formed, it would have a methyl group in the critical position to each phenyl radical, which is not the case with the di-ethyl ketone compound, (I.) :—

(I.)



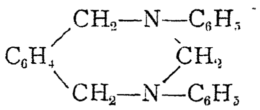
(II.)



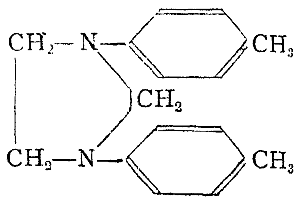
[1] Vorlander, *Ber.*, **30**, 2261 (1897)

Scholtz and Jaross,[1] following out some observations of Bischoff,[2] showed that the action of formaldehyde on diamines was greatly influenced by stereochemical phenomena. They were able to form the rings I. to VI., but no ring-formation could be produced in the case of the compounds VII. to X.

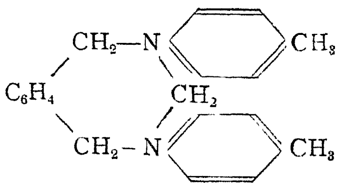
(I.)



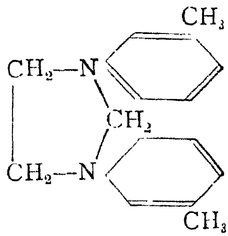
(IV.)



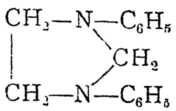
(II.)



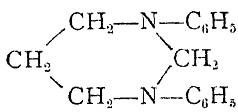
(V.)



(III.)



(VI.)



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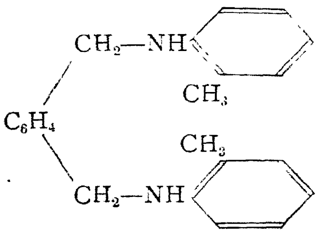
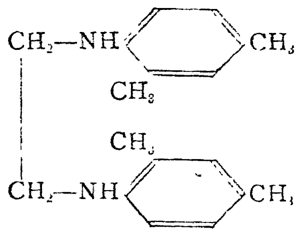
[1] Scholtz and Jaross, *Ber.*, **34**, 1504 (1901).
[2] Bischoff, *ibid.*, **31**, 3255 (1898).

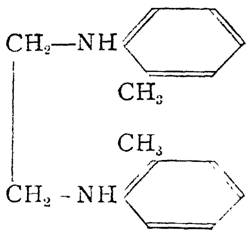
(VII.)



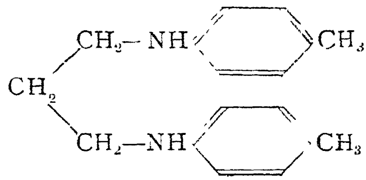
(IX.)



(VIII.)



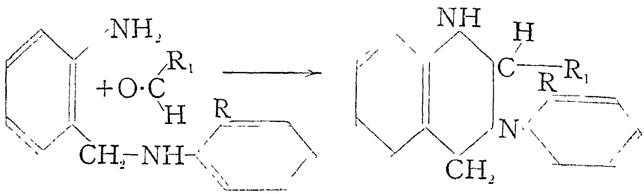
(X.)



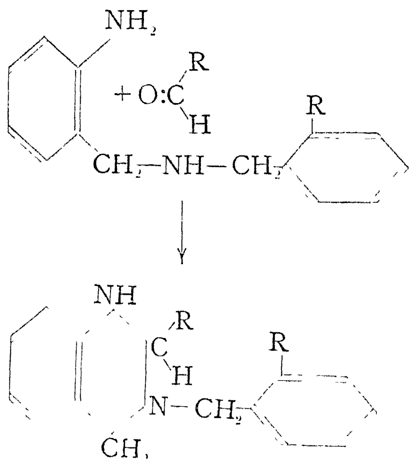
The influence of the methyl group when in the ortho-position and its indifference when in either the meta- or para-positions is well marked in these results. Of course, the phenyl groups are free to swing about their axes, but this rotation will bring the methyl group into a position to hinder ring-formation during at least half the time. Further investigation showed that acetaldehyde could form a ring corresponding to (V.) and propaldehyde one similar to (X.); while carbonyl chloride formed cyclic compounds of the types (IV.) and (V.), but not one like (VIII.).

Some work by Busch shows that there can be no doubt that such hindrances are due to stereochemical causes. He found that by choosing his reagents in such a way as to remove the hindering group from the immediate neighbourhood of the atoms concerned in the ring-formation, no difficulty was encountered. For example, the influence of the substituent R

is very strongly marked in the case of the reaction (a condensation with an aldehyde) schematically represented below:—[1]



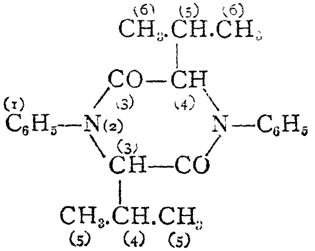
But if a methylene group be introduced between the nitrogen atom and the phenyl nucleus, the ortho-substituent is removed to such a distance that it has but little effect upon the reaction.



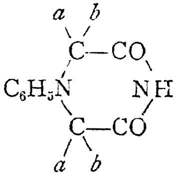
In the syntheses of piperazine derivatives, Bischoff[2] noticed two cases in which the introduction of substituents caused hindrance to the formation of a ring. In trying to condense two molecules of α-bromo-isovalerianic anilide to form the ring shown below, he found that no condensation took place: he

[1] Busch, *J. pr. Chem.*, [2] **55**, 357 (1897).
[2] Bischoff, *Ber.*, **30**, 2319 (1897).

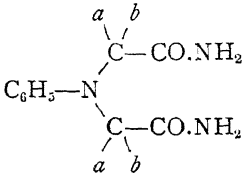
explains this on the Dynamic Hypothesis, since had the compound been formed, the phenyl groups would have been in the position 1,5 and 1,6 to the methyl radicals :—



Bischoff[1] also found a more general case when the substituents are differently placed. The ring (I.) can only be formed when *a* and *b* are hydrogen atoms; if either *a* or *b*, or both, be changed to methyl, the ring is not produced, but, instead, a compound of the type (II.) results. Here, again, the hindering groups stand in the position 1,5 to one another :—

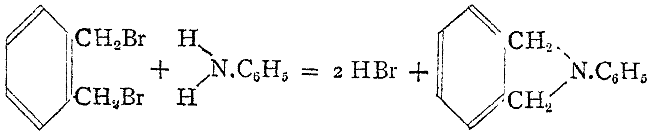


(I.)



(II.)

Xylylene bromide reacts with aniline to form a ring compound :—

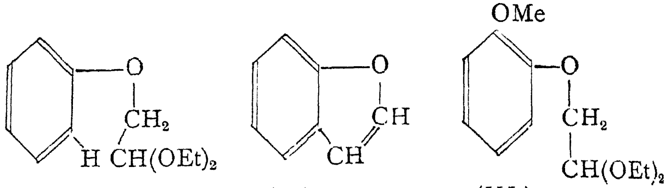


Now, when ortho-substituted anilines are used (*o*-toluidine,

[1] Bischoff, *Ber.*, **30**, 2310 (1897).

o-xylidine, or *o*-pseudocumidine), no ring is formed; though with *m*- or *p*-substituted aniline there is no difficulty. *a*-Naphthyl-amine, *o*-chloro-, and *o*-bromo-aniline also fail to form the ring. The ortho-substituent evidently acts as a hindering influence, but if it be removed far enough from the sphere of action of the amido-group, as in the case of *o*-tolu-benzylamine, no hindrance is observed. Similar results are obtained when trimethylene bromide is substituted for xylylene bromide.[1]

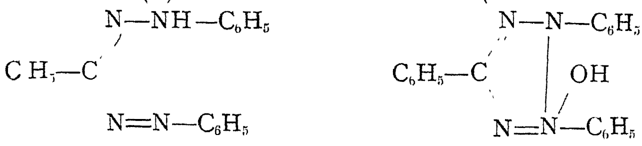
When phenoxy-acetals, (I.), are boiled with dilute sulphuric acid they condense to cumarone derivatives, (II.); but if there be a methoxy-group in the ortho-position to the side chain, (III.), the reaction does not take place :—[2]



(I.) (II.) (III.)

Another case of intramolecular ring-formation is to be found in the tetrazolium derivatives.[3] Formazyl-benzene, (I.), can be oxidised to triphenyl-tetrazolium hydroxide, (II.). But if the phenyl groups attached to the nitrogen atoms have ortho-substituents, the reaction proceeds much more slowly than would otherwise be the case; while an even greater effect is noticed when substituents are introduced into the phenyl nucleus which is attached to a carbon atom :—

(I.) (II.)

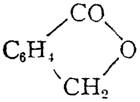


[1] Scholtz, *Ber.*, **31**, 414, 627, 1154, 1707 (1898); **32**, 2251 (1899).
[2] Stormer, *Annalen*, **312**, 334 (1900).
[3] Wedekind and Stauwe, *Ber.*, **31**, 1746 (1898).

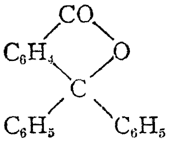
We must now turn to the second branch of the subject, and consider the effect of substitution upon the stability of cyclic compounds.

In the case of carbocyclic compounds, the effect of substitution is not very uniform, since in some cases it appears to diminish the stability, while in others it increases it.[1] Space relations appear, however, to play some part in the matter; for Buchner[2] found that the more symmetrically substituted trimethylenes were less liable to an opening of the ring than those in which the substituents were unsymmetrically placed about the plane of the ring, while Gustavson and Popper[3] observed that symmetry had a greater influence than chemical character in the substituent.

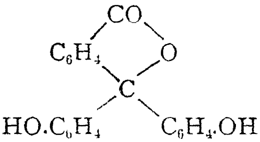
Sometimes the introduction of new radicals into a compound tends to make it less stable than before, as in the case of methyl-furan, which, when treated with hydrochloric acid in methyl alcohol, is much more easily opened up than furan itself.[4] But, on the other hand, Hjelt[5] found that the stability of the phthalide ring was increased by substitution, phenolphthalein being more stable than diphenylphthalide, and this in turn being more stable than phthalide :—



Phthalide (least stable).



Diphenyl-phthalide (more stable).



Phenolphthalein (most stable).

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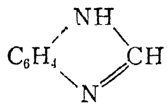
[1] Kotz, *J. pr. Chem.*, [2] **68**, 174 (1903).
[2] Buchner, *Annalen*, **284**, 202 (1895).
[3] Gustavson and Popper, *J. pr. Chem.*, [2] **58**, 458 (1898).
[4] Harries, *Ber.*, **31**, 37 (1898).
[5] Hjelt, *Chem. Zeit.*, **18**, 3 (1894).

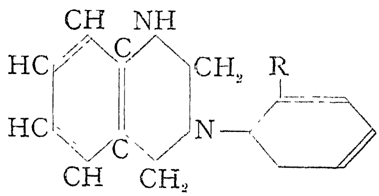
The influence of space arrangement is perhaps shown in the case of derivatives of imidazol :—



Benzimidazol.

in which hydrolysis with sodium hydroxide is hindered by the presence of a substituent on the carbon atom between the two nitrogens, or by methyl radicals on the benzene nucleus. Radicals on the two nitrogen atoms also hinder the opening of the ring, their influence being proportional to their size.[1]

Busch[2] found that in compounds of the phenyl-tetrahydroquinazoline series, an ortho-substituent, R, has the effect of increasing the stability of the substance :—



To these qualitative investigations may be added notes on several instances, which have been quantitatively studied.

Miolati[3] examined the case of substitution in the succinimide derivatives. Substitution in the ring increases the stability, as methyl-succinimide hydrolyses only half as fast as succinimide itself; from the following table it will be seen, however, that the introduction of alkyl groups attached to the nitrogen atom tends to decrease the stability of the imides :—

[1] Fischer and Rigaud, *Ber.*, 34, 4202 (1901).

[2] Busch, *J. pr. Chem.*, [2] 55, 357 (1897).

[3] Miolati, *Atti R. Accad. Lincei*, [5] 3, II., 515 (1894); Miolati and Longo, *ibid.*, 597 (1894); 4, I., 351 (1895); Miolati and Lotti, *ibid.*, 5, I., 88 (1896); compare Piutti, *Ber.*, 29, 85 (1896).

Name.	Hydrolysis coefficient
Succinimide	0·002382
Methylimide	0·2263
Ethylimide	0·08426
n-Propylimide	0·0550
i-Propylimide	0·06781
sec. Butylimide	0·03723
i-Butylimide	0·03885

Even better examples of stereochemical influences are to be found in the case of the substituted phenyl derivatives of succinimide :—[1]

Name.	Hydrolysis coefficient.
Phenylsuccinimide	2·2681
o-Tolylsuccinimide	0 8558
m- ,,	1·098
p- ,,	1·1210
2,3-Dimethylphenylsuccinimide	0·8147
3,4- ,, ,,	1·270
2,4- ,, ,,	0·8653
3,5- ,, ,,	1·145
2,6- ,, ,,	0-1571
2,5- ,, ,,	0·8757

The effect of the ortho-methyl group is very marked when compared with that of the meta- and para- substituents. The opening of the succinimide ring has also been studied by Gilbody and Sprankling.[2] It would seem that substitution in the fatty ring tends to decrease the stability, while substitution in the aromatic nucleus increases it.

The foregoing instances will be sufficient to show that in certain reactions substituents can exert a hindering influence. In other cases it was found that the presence of substituted groups facilitated the formation of a cyclic compound. A few of these will now be described.

The formation of an anhydride of a dicarboxylic acid takes

[1] Miolati and Lotti, *Atti R. Accad. Lincei*, [5] **5**, I., 88 (1896).

[2] Gilbody and Sprankling, *Proc.*, **16**, 224 (1900).

place with more or less ease according as the carboxyl groups are near to or far apart from one another. Cases of this kind have been dealt with in the unsaturated acids, where the one stereoisomer loses water much more readily than the other. In that case the proximity of the carboxyl groups is conditioned by the presence of the double bond, but it has been found possible to produce a similar approach by means of substitution. If we consider the different substituted maleic acids, we shall find that, as a rule, the more substituents we introduce the more readily does the acid form an anhydride; the following acids may be mentioned:—

$\begin{array}{r} H-C-COOH \\ \Vert \\ H-C-COOH \end{array}$	Stable: anhydride produced on distillation.
$\begin{array}{r} CH_3-C-COOH \\ \Vert \\ H-C-COOH \end{array}$	Anhydride produced under 100° C
$\begin{array}{r} CH_3-C-COOH \\ \Vert \\ Br-C-COOH \end{array}$	Anhydride produced on standing over sulphuric acid.
$\begin{array}{r} Br-C-COOH \\ \Vert \\ Br-C-COOH \end{array}$	Anhydride produced at ordinary temperatures.
$\begin{array}{r} C_2H_5-C-COOH \\ \Vert \\ C_2H_5-C-COOH \end{array}$	Known only in form of anhydride

It seems as if the introduction of bulky groups tended to press the carboxyl groups nearer together in the molecule, and hence to facilitate the elimination of water.

Similar results are found in other series. Glutaric acid boils almost without decomposition at 303–5° C, methyl and ethyl-glutaric acids partly break down into anhydrides, while iso-trimethyl-glutaric acid gives an anhydride merely on boiling with water.

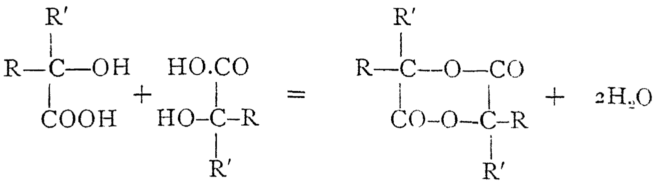
Hjelt[1] has studied quantitatively the relative amounts of anhydrides formed from the substituted succinic acids after an hour's heating to various temperatures. His results are as follows:—

[1] Hjelt, *Ber.*, **26**, 1925 (1893).

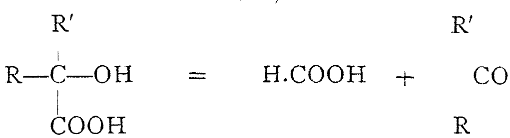
Succinic acid	6·7	per cent. at	200° C.
Methyl-succinic acid	42·9	,,	200° C.
,, ,,	18·9	,,	170° C.
,, ,,	14·1	,,	160° C.
Ethyl-succinic acid	14·5	,,	160° C.
n-Propyl-succinic acid	16·6	,,	160° C.
Iso-propyl-succinic acid	29·9	,,	160° C.

It must be observed that not only the size of the radicals which are introduced into a compound, but also their nature, and possibly also their mode of vibration, have an influence upon the amount of hindrance they produce. α-Hydroxy-carboxylic acids may react in two ways in presence of dehydrating agents: they may form a ring as in (I.), or may break down into an acid, a ketone, or aldehyde, or other products, (II.) :—

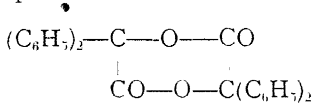
(I.)



(II.)

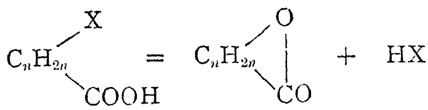


Now, it has been noticed that the six-membered ring is formed only when either R or R′ is a hydrogen atom; for example, when both of them are methyl groups no ring is produced. But it has been found that benzilic acid yields an anhydride which appears to possess the formula :—



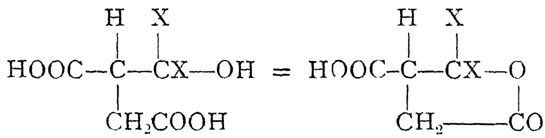
so that in this case a phenyl group does not appear to have so great a hindering effect as a methyl radical.

Lactones may be formed from halogen-substituted acids by loss of halogen acids :—



and Freer[1] has found that in this case also the introduction of substituents, if carried far enough, suffices to bring about a spontaneous formation of lactones in the case of the γ-halogen substituted acids.

Fittig[2] and Hjelt[3] have shown that in the conversion of the dibasic hydroxy-acids into lactonic acids :—



most time is required when X is a hydrogen atom. Phenyl increases the reaction speed four times, methyl eight times, and isobutyl sixteen times. When the two X radicals are methyls, the resulting compound forms a lactone twice as fast as when the X groups are ethyl and a hydrogen atom.

Bischoff[4] has shown that similar relations hold in the case of lævulinic acid and its homologues. Further investigation by Bischoff and Walden[5] led to the following results. The figures give the percentage of lactone formed by each acid under the given conditions :—

---

[1] Freei, *Annalen*, **319**, 351 (1901).
[2] Fittig, *ibid*, **238**, 197 (1887).
[3] Hjelt, *Acta Soc. scient. fennicæ*, **18**, 1 : **19**, 13.
[4] Bischoff, *Ber.*, **23**, 621 (1891).
[5] Bischoff and Walden, *ibid.*, **26**, 1452 (1893).

After minutes.	Lævulinic acid.	α-Methyl lævulinic.	α-Dimethyl lævulinic.	α-Ethyl lævulinic.
15	7·63	20·48	27·86	37·24
30	13·09	29·85	31·96	44·26
45	21·54	33·99	35·62	47·95
60	26·57	48·88	—	58·63

A study of these instances shows that the presence of substituent groups may play a very considerable part in those reactions which lead to the formation of ring-compounds. In certain cases the substituents exercise a hindering effect upon the reactions, while in other instances they appear to favour the formation of the ring. In the first case, we are dealing with a phenomenon, similar in some respects to the examples of chain formation dealt with in the previous chapter ; the second case resembles the decomposition reactions which have already been described.

CHAPTER IV.

THE CONFIGURATION OF OPTICALLY INACTIVE CARBON COMPOUNDS.

§ I. *THE SHAPE OF CARBON CHAINS.*

IN this chapter, two questions will be studied: first, that of the shape which a carbon open chain normally assumes in space; and, second, that of the configuration of the molecule in open-chain compounds. In the first section, we have to decide whether a series of carbon atoms linked together by single bonds will lie in a straight line, in a zig-zag form, or in a more or less cylic figure; while in the second section we must apply to inactive carbon compounds processes analogous to some extent to those which we used in the determination of the configurations of the various sugars.

When we examine the structural formula of any paraffin compound:—

$$\overset{1}{CH_3}—\overset{2}{CH_2}—\overset{3}{CH_2}—\overset{4}{CH_2}—\overset{5}{CH_2}—\overset{6}{CH_2}—\overset{7}{CH_2}\ .\ .\ .$$

we should conclude from such a formula that the atoms marked 1 and 2 were much nearer together than 1 and 3, or any higher number; and, in consequence, we should expect to find that a reaction between groups attached to 1 and 2 would proceed with greater ease than if the reacting groups were attached to, say, the atoms 1 and 7.

On the other hand, if we assume that the four groups attached to a carbon atom are tetrahedrally arranged in space, the problem assumes quite a different aspect, for then we should find, as was mentioned in Chapter II. of this part, that

the atoms 1 and 5 are nearer together in space than any others, the distances being :—

Between A and B .	1·00
„ A and C	1·02
„ A and D .	0·67
„ A and E .	0·07

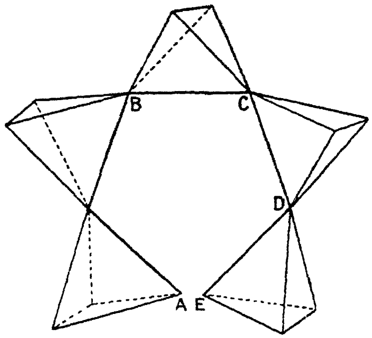


FIG. 49.

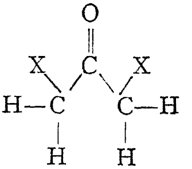
The experimental material which was dealt with in Chapter II. certainly favours the second view rather than the first, for there it was shown that when the two reactive groups lay in the 1,5- or 1,6-positions with regard to each other their tendency to react was greater than when they were situated nearer together in the chain; and the same may be said for the results described in the section of Chapter I. upon Chain Formation, in which the influence of the 1,5- and 1,6-positions was also marked.

For some time, however, P. Petrenko-Kritschenko[1] has

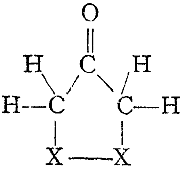
[1] Petrenko-Kritschenko, *J. pr. Chem.*, [2] **61**, 431 (1900); **62**, 315 (1900). Petrenko-Kritschenko and E. Eltschaninoff, *Ber.*, **34**, 1699 (1901) Petrenko Kritschenko and S. Lordkipanidze, *ibid.*, **34**, 1702 (1901) Petrenko-Kritschenko and E. Eltschaninoff, *J. Russ. Phys. Chem. Soc.*, **35**, 146 (1903). Petrenko-Kritschenko and A. Konschin, *ibid.*, **35**, 404 (1903). Petrenko-Kritschenko and E. Kestner, *ibid.*, **35**, 406 (1903). Petrenko-Kritschenko and T. Dolgopoloff, *ibid.*, **36**, 1505 (1905)

been working with the purpose of showing that the current view is incorrect; and it seems desirable to discuss his results in order to see how far his deductions from them are justified.

His earlier papers were based upon the following hypothesis. It has been shown by Menschutkin and others that the reactivity of a cyclic compound is usually greater than that of its aliphatic analogue; and this Petrenko-Kritschenko endeavoured to explain by assuming that the ring structure tended to remove the groups nearest the reactive radical from its sphere of action, and so diminished the steric hindrance to its activity. A concrete example will make this clear. If we consider the case of the ketonic compounds (I.) and (II.):—



(I.)

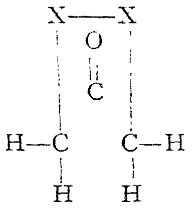


(II.)

it is evident that in the compound (I.) the reactions of the carbonyl group will be subjected to steric hindrance from the groups X, for since free rotation will exist around the carbon atoms to which the X groups are attached, these X groups are certain, sooner or later, to vibrate into the positions shown in the first figure. On the other hand, if we join the two X groups together, thus forming the cyclic compound (II.), the steric hindrance due to them will be much less than in the last case. This can be seen by comparing the formulæ (I.) and (II.); it will be seen that in (II.) the X groups are much further removed from the sphere of action of the carbonyl group than they are in (I). It may be objected that compound (II.) might be written thus:—

Petrenko-Kritschenko, *Annalen*, **341**, 150 (1905). Petrenko-Kritschenko and A. Konschin, *ibid.*, **342**, 51 (1905). Petrenko-Kritschenko and A. Konschin, *J. Russ. Phys. Chem. Soc.*, **37**, 1127 (1906). Petrenko-Kritschenko and W. Kantscheff, *Ber.*, **39**, 1452 (1906).

(III.)



in which case the steric hindrance would seem to be increased by the ring-formation. If a model be constructed, however, it will be found that (III.) is a very strained and improbable configuration. So far, then, we may admit that Petrenko-Kritschenko's views are correct. Undoubtedly the steric hindrance in the case of the cyclic compound would be less than in the corresponding open-chain derivative.

We must now see what method Petrenko-Kritschenko used in order to determine the relative degree of hindrance experienced in the two cases. Since he was dealing with ketones, it seemed natural to employ the ordinary ketonic reactions, which lead either to addition compounds or to products in which the oxygen of the carbonyl group is exchanged for various radicals; and, in point of fact, he utilised the formation of bisulphite compounds, of oximes, and of phenylhydrazones :—

$$\begin{matrix} R \\ R' \end{matrix}\!\!>\!C{:}O \;+\; KHSO_3 \;=\; \begin{matrix} R \\ R' \end{matrix}\!\!>\!C\!<\!\!\begin{matrix} SO_3K \\ OH \end{matrix}$$

$$\begin{matrix} R \\ R' \end{matrix}\!\!>\!C{:}O \;+\; NH_2OH \;=\; \begin{matrix} R \\ R' \end{matrix}\!\!>\!C{:}N.OH \;+\; H_2O$$

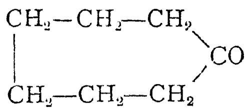
$$\begin{matrix} R \\ R' \end{matrix}\!\!>\!C{:}O \;+\; NH_2NH.C_6H_5 \;=\; \begin{matrix} R \\ R' \end{matrix}\!\!>\!C{:}N.NH.C_6H_5 \;+\; H_2O$$

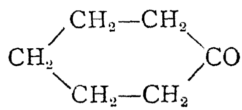
When we consider how steric hindrance can best be measured, it becomes apparent that we should endeavour to

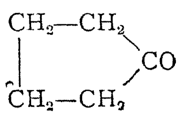
estimate the initial velocity of the reaction we are studying, and not merely ascertain the gross amount of product which is formed after an arbitrary time has elapsed. It has been shown by Menschutkin that the initial velocity and the total amount of substance formed after the reaction has run its course do not stand in any simple relation to one another. Petrenko-Kritschenko, however, merely measured the amount of reaction product which he obtained after the lapse of one hour. Such a method, when applied to reversible reactions such as the formation of bisulphite compounds, can yield no very valuable results. His figures may be quoted, however, for the sake of comparison with those he obtained later by other methods :—

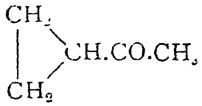
$CH_3.CO.CH_3$	22 per cent.
$CH_3.CO.CH_2.CH_3$	14 „
$CH_3.CO.CH_2.CH_2.CH_3$	12·4 „
$CH_3.CO.CH_2.CH_2.CH_2.CH_2.CH_2.CH_3$	5·7 „
$CH_3.CO.CH(CH_3)_2$.	2·7 „
$CH_3.CH_2.CO.CH_2.CH_3$	1·8 „
$CH_3.CH_2.CO.CH_2.CH_2.CH_3$. . . .	2·0 „
$CH_3.CH_2.CH_2.CO.CH_2.CH_2.CH_3$ . .	0·0 „

The results obtained in a similar manner for the cyclic ketones were :—

 . . . . . . 4·8%

 . . . . . . 35·0%

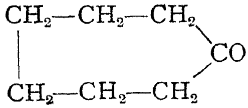
 . . . . 7·0%

 0%

From these figures it appears that in most cases the cyclic compound is more reactive than its aliphatic analogue. As we have stated, however, too much reliance cannot be placed upon them, owing to the hydrolysis which takes place during the time of reaction.

The results which Petrenko-Kritschenko obtained by using hydroxylamine instead of potassium bisulphite are probably much more accurate. His method in this reaction was as follows. A milligramme molar solution of hydroxylamine in water was placed in a 100-c.c. flask and diluted with an equal weight of alcohol. The flask was then placed in water of ordinary "room temperature" for twenty minutes, after which a corresponding quantity of a milligramme molar solution of a ketone in 50 per cent. alcoholic solution was added. Thereafter the flask was filled up to the mark with 50 per cent. alcohol, shaken, and allowed to stand for an hour. At the end of this time the remaining hydroxylamine was estimated by titration. By this means the following figures were obtained. They represent percentages of oxime formed in one hour:—

$CH_3.CO.CH_3$ . . .	82
$CH_3.CO.CH_2.CH_3$ . . .	79·2
$CH_3.CO.CH_2.CH_2.CH_3$.	74·6
$CH_3.CH_2.CO.CH_2.CH_3$	37·9
$CH_3.CH_2.CO.CH_2.CH_2.CH_3$ . .	36·8
$CH_3.CH_2.CH_2.CO.CH_2.CH_2.CH_3$	31·4
$CH_3.CO.CH_2.CH_2.CH_2.CH_2.CH_2.CH_3$	67·6
$CH_3.CO.CH(CH_3)_2$ . . .	33·0
$CH_3.CH_2.CO.CH(CH_3)_2$	28·9
$C_6H_5.CO.CH_3$ . .	9·2
$C_6H_5.CHO$ . . .	85·0
$(CH_3)_2.CH.CHO$	76·7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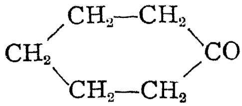
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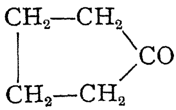
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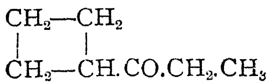
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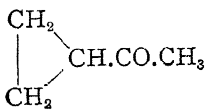
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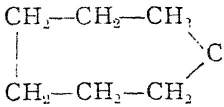
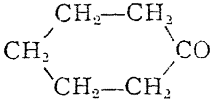
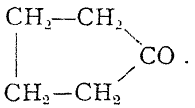
The reaction between ketones and phenylhydrazine was carried out similarly to that with hydroxylamine; and the surplus phenylhydrazine was estimated by the method of E. Meyer.[1] The percentage results obtained are as follows:—

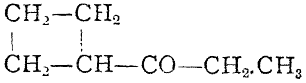
$CH_3.CO.CH_3$		66
$CH_3.CO.CH_2.CH_3$		52
$CH_3.CO.CH_2.CH_2.CH_3$		38
$CH_3.CO.CH_2.CH_2.CH_2.CH_2.CH_2.CH_3$		31
$CH_3.CO.CH(CH_3)_2$		15
$CH_3.CO.C(CH_3)_3$		3·6
$CH_3.CH_2.CO.CH_2.CH_3$		11
$CH_3.CH_2.CO.CH_2.CH_2.CH_3$		10
$CH_3.CH_2.CO.CH(CH_3)_2$		3·7
$CH_3.CH_2.CH_2.CO.CH_2.CH_2.CH_3$		7·5
$C_6H_5.CO.CH(CH_3)_2$		0·5
$CH_3.CO.CH_2.CH_2.CO.CH_3$	one molecule	22·7
	half-molecule	17·9

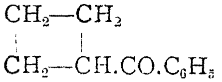
[1] E. Meyer, *J. pr. Chem.*, [2], **36**, 115 (1887).

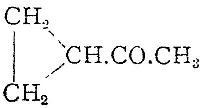
 . . . . 26·9

 . { one molecule 39·7; half-molecule 56 }

 . . . . 42·3

 . . . . 7·5

 . . . . . 1·2

 . . . . 5·6

From these figures it is clear that at the end of an hour a much greater quantity of reaction product is present in the case of the cyclic ketones than in that of the analogous open-chain compounds. Petrenko-Kritschenko ascribes this to the removal of the atoms of the cyclic chain from the sphere of influence of the carbonyl group in the manner explained before; but in view of the fact that cyclic compounds are much more tautomeric than open-chain ones, the theory of the nascent carbonyl group * appears to afford a much more probable explanation of his results.

There are other ways in which the problem may be approached. For instance, Massol[1] employed the following

* See p. 316.

[1] Massol, *Compt. rend.*, **130**, 338 (1900).

method. He measured the heats of neutralisation with caustic potash of a series of open-chain dibasic acids, beginning with malonic acid and going up the homologous series till he came to sebacic acid, which has a chain of eight methylene groups between the two carboxyl radicals. His results, calculated from the equation :—

$$C_nH_{2n-2}O_4 + 2KOH = C_nH_{2n-4}O_4K_2 + 2H_2O + Q$$

are as follows, the quantity Q being expressed in great calories :—

		Q
Malonic acid . .	$COOH.CH_2.COOH$ . .	48·57
Succinic acid . .	$COOH.(CH_2)_2.COOH$.	46·40
Glutaric acid . .	$COOH.(CH_2)_3.COOH$.	44·23
Adipic acid . .	$COOH.(CH_2)_4.COOH$.	45·45
Pimelic acid . .	$COOH.(CH_2)_5.COOH$.	45·45
Suberic acid . .	$COOH (CH_2)_6.COOH$.	44·76
Azelaic acid .	$COOH.(CH_2)_7.COOH$	44·76
Sebacic acid . .	$COOH.(CH_2)_8.COOH$.	43·99

From these results it appears that the five-membered chain has no particular advantage over its fellows; but that, instead, there is a steady decline in value, as the carboxyl groups are set further apart.

In another volume of this series[1] it was shown that in considering the conductivity of a dibasic acid from the point of view of the problem before us, we had to consider the *second* ionisation-constant rather than the first. The figures given in that place for the second ionisation-constants of various acids support Massol's results, as there seems to be no special value to distinguish the five-membered chain from the others. It should be noted that an increase in the second ionisation-constant indicates that the carboxyl groups are being removed further from each other in space.

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[1] *Electro-Chemistry*, Part I., by R. A. Lehfeldt, pp. 112–117.

		$K_2 \times 10$
Malonic acid .	$COOH.CH_2.COOH$ . . .	1·0
Succinic acid .	$COOH.(CH_2)_2.COOH$ . .	2·3
Glutaric acid .	$COOH.(CH_2)_3.COOH$.	2·7
Adipic acid	$COOH.(CH_2)_4.COOH$.	2·4
Pimelic acid . .	$COOH.(CH_2)_5.COOH$.	2·6
Suberic acid . .	$COOH.(CH_2)_6.COOH$.	2·5

A general discussion of the question as far as it concerns the halogen-substituted acids is to be found in a paper by Freer.[1] The original, being chiefly polemical, need not be dealt with in detail here; the results arrived at were as follows:—

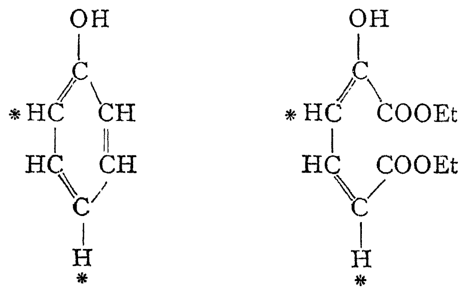
$$\begin{array}{ccccccccc} — & C & — & C & — & C & — & C & —COOH \\ & | & & | & & | & & | & \\ & \delta & & \gamma & & \beta & & \alpha & \end{array}$$

The influence of the halogen atom on the carboxyl group can be regarded as the sum of two factors. The first factor depends upon the number of carbon atoms in the carbon chain, an increase in the length of the chain reducing the strength of the acid. The second factor concerns the actual distance *in space* between the halogen and carboxyl, and its influence is shown in the rapidity with which halogen atoms in the γ-position can be hydrolysed. If we judge from the effect of the first factor alone, the γ-position is further away from the carboxyl than the α-position; but, if we take the second factor alone into account, the reverse seems true. In comparison with the γ-compounds, the δ-chlorine, bromine, and iodine derivatives of valerianic acid show a decrease in initial conductivity; so that here the influence of the number of carbon atoms in the chain makes itself felt. The δ-acids, too, hydrolyse much more slowly than the γ-derivatives; and since it is found that in this respect the δ- and β-acids both have less activity than the γ-ones, the γ-position must be supposed to be nearer

[1] Freer, *Annalen*, **319**, 345 (1901).

in space to the α-position than is the case with either the β- or the δ-position.

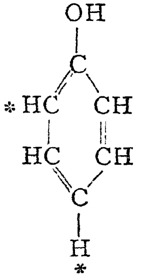
Prager[1] attacked the problem from another side. Starting from the fact that phenol has the faculty of coupling with diazo-benzene, he traced this to the structure of phenol; and then endeavoured to find an analogous aliphatic substance. This he discovered in the compound oxalo-crotonic ester, for, as can be seen by comparing the formulæ, the two have very similar structures:—

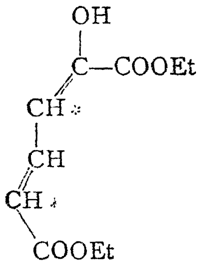


He found that oxalo-crotonic ester did react with diazo-benzene, and *two* of the hydrogen atoms in it could be replaced by the diazo-benzene radical. These two atoms are marked with asterisks in the formula, and for the sake of comparison those of the phenol which can be replaced in the same way are also marked. So far, however, no proof had been obtained that the special grouping had much to do with the reaction, as it might have been attributed to the presence of the double bond in both compounds. Prager was able to show that no reaction took place with either crotonic ester, $CH_3.CH:CH.COOEt$, or sorbic acid, $CH_3.CH:CH.CH:CH.COOH$. Since the latter contains the proper arrangement of double bonds, it is evident that they alone are not concerned in the matter. The only remaining factor is the hydroxyl group. Now, in phenol the diazo-radical enters the para-position first, and then afterwards the ortho-position; in oxalo-crotonic ester these

[1] Prager, *Annalen*, **338**, 360 (1905).

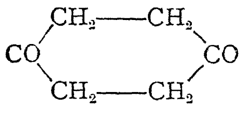
conditions are reversed. This, however, is a secondary matter; the main point is that in both compounds the hydrogen atoms in the same relative positions in the chain are attacked. If, however, we write the formula for oxalo-crotonic ester in the zig-zag form, there is practically no resemblance between it and phenol; certainly the resemblance between the two compounds is not nearly so clear as it is in the first two formulæ:—





This evidence may not be very strong, but it certainly favours the view that the open-chain compound resembles its cyclic analogue in configuration. Its weak point lies in the tacit assumption that, in this reaction, the configuration plays a greater *rôle* than the structure.

In the course of some work which has not yet been published, Baly and Stewart made an observation which, as as far as it goes, appears to be in disagreement with the view that open and closed chains have similar configurations in space. It was stated by Hartley and Dobbie[1] that diketo-hexamethylene:—

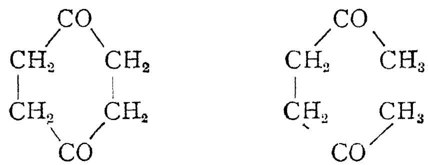


showed no selective absorption. As this did not agree with the views of Baly and Stewart, they repeated the experiments,

[1] Hartley and Dobbie, *Trans.*, **73**, 598 (1898).

using a specimen of diketo-hexamethylene kindly furnished by Prof. W. H. Perkin, jun. The results with this compound were different from those arrived at by Hartley and Dobbie, as it was found that the spectrum contained a long absorption band, having its head at 3550, and extending from 20 mm. to 5 mm. of an N/10 solution. It was also noticed that this band was eliminated when hydrochloric acid was added to the solution; and on referring to Hartley and Dobbie's paper it appeared that their substance, from the method of preparation, probably contained traces of sulphuric acid, which would account for their failing to obtain the band in their photographs.

Now, if we write the formulæ of acetonylacetone and diketo-hexamethylene side by side, it will be seen that they are analogous in form :—



We should, therefore, expect to find a similarity in their spectra, if Prager's view be correct. There is, however, very small resemblance between the two compounds in this respect, for while diketo-hexamethylene has an absorption band of great persistence, the band in acetonylacetone is remarkable for its shallowness.[1] The results of Petrenko-Kritschenko are here in agreement with those described above, as he found that the reactivity of the carbonyl radical in acetonylacetone was very low in comparison with that of diketohexamethylene. Thus, if we allow Prager's assumption that configuration and not structure determines the reactivity of certain radicals, the spectroscopic evidence is not in favour of a cyclic configuration for such a compound as acetonylacetone.

It has been mentioned that Heyl and Victor Meyer[2] showed

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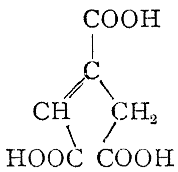
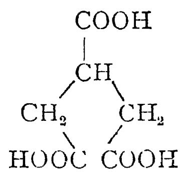
[1] Stewart and Baly, *Trans.*, **89**, 489 (1906).

[2] Heyl and V. Meyer, *Ber.*, **28**, 2776 (1895).

that in the cases of aconitic and tricarballylic acids, no hindrance to the esterification process was apparent. This, also, might be adduced as evidence in favour of the cyclic configuration of the chain; for if the formulæ of these acids be written in a cyclic form, it will be seen that the carbon atoms of two carboxyl radicals lie in the 1,5-position to each other, and would therefore be far removed from the third carboxyl group which lies at the centre of the chain :—



Aconitic acid.

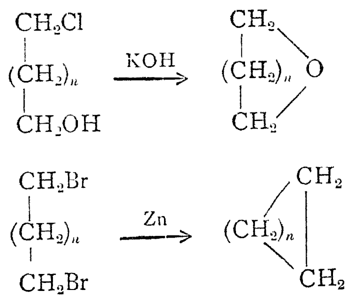


Tricarballylic acid.

The strongest evidence in favour of the cyclic view, however, has already been dealt with in the chapter on Chain Formation. When we consider the enormous amount of material which has been gathered together in favour of the Dynamic Hypothesis, it seems certain that some peculiar relation exists between the positions 1 and 5, or 1 and 6 of a carbon chain; and since these positions are the ones which would most probably be adjacent if the chain were cyclic in form, there seem to be strong grounds for supposing that the chain does assume the ring shape, or, at any rate, vibrates into this form at very frequent intervals.

Another series of experiments must be described, however, which point to a different conclusion. Petrenko-Kritschenko and Konschin,[1] with whose results those of Evans, given later in this chapter, should be compared, have measured the velocity of the two reactions, (*a*) between glycol monochlorhydrins and caustic potash, and (*b*) between alkyl dibromides and zinc dust :—

[1] Petrenko-Kritschenko and Konschin, *Annalen*, **342**, 51 (1905).



The constants were calculated from the usual equation for a bi-molecular reaction. The method and results are given below.

One milligramme-molecule of the chlorohydrin, and one milligramme-molecule of caustic potash were dissolved in 100 c.c. of aqueous alcohol, of such a strength that after the mixture of the alkali and chlorohydrin was complete, the concentration of alcohol in the solution amounted to 54 per cent. The temperature was 24·9° C. The results were :—

	t Minutes.	x Per cent	K
Ethylene chlorohydrin, $CH_2Cl.CH_2OH$	15	16·85	0·01351
	30	29·60	0·01401
	45	37·39	0·01327
	60	43·62	0·01289
γ-Pentylene chlorohydrin, $CH_3.CHCl.CH_2.CH_2.CH_2OH$	15	4·15	--
	30	5·19	0·00076
	45	6·75	0·00097
	60	7·78	0·00091

In the next series of experiments the method was varied slightly. One milligramme-molecule of the chlorohydrin was mixed with ten milligramme-molecules of caustic potash in 100 c.c. of aqueous alcohol. The alcohol concentration after the mixture was 48 per cent. The temperature in this case also was 24·9° C. :—

	t Minutes.	*x* Per cent.	K
Trimethylene chlorohydrin, $CH_2Cl.CH_2.CH_2OH$	30	0·52	0·00017
	45	1·04	0·00021
	60	1·56	0·00026
γ-Pentylene chlorohydrin	30	21·29	0·00854
	45	28·56	0·00858
	60	32·70	0·00763
δ-Hexylene chlorohydrin, $CH_3.CHCl.CH_2.CH_2.CH_2.CH_2OH$	30	10·4	0·00041
	45	10·9	0·00041
	60	11·0	0·00028

Under similar conditions, with the exception that the temperature was raised to 69·7° C., the following results were obtained:—

	t Minutes	*x* Per cent	K
Trimethylene chlorohydrin	15	2·08	0·00142
	30	4·15	0·00144
	45	6·23	0·00147
	60	7·78	0·00140
δ-Hexylene chlorohydrin (undistilled)	15	21·8	—
	30	23·9	0·00235
	45	25·44	0·00208
	60	25·44	0·00135
δ-Hexylene chlorohydrin (distilled)	15	11·41	—
	30	14·54	0·00275
	45	16·60	0·00234
	60	18·17	0·00207

By these results, Petrenko-Kritschenko is convinced that there is a sudden fall in the velocity of the reaction when the α-compound is replaced by the β-one; and that no great difference seems to exist between the other members of the series, although the γ-compound appears to have a slightly higher reaction velocity than its neighbours.

The method employed in the case of the reaction between

zinc dust and the alkyl dibromides was as follows. One milligramme-molecule of the dibromide and one milligramme-atom of zinc dust were mixed in a flask with 100 c.c. of 50 per cent. alcohol. The mixture was shaken for an hour (or six hours) in water of temperature between 18° C. and 19° C. At the end of fixed times, the amount of reaction product was estimated. The following results were obtained:—

		1 hour. Per cent.	6 hours. Per cent.
Ethylene bromide . .	$CH_2Br.CH_2Br$	19·87	—
Propylene bromide . .	$CH_2Br.CHBr.CH_3$ . .	20·87	53·58
Trimethylene bromide .	$CH_2Br.CH_2.CH_2.Br$ . . .	2·02	2·60
γ-Pentylene bromide .	$CH_3.CHBr.CH_2.CH_2.CH_2Br$.	1·80	1·55
Pentamethylene bromide	$CH_2Br.CH_2.CH_2.CH_2.CH_2Br$.	1·25	1·04
δ-Hexylene bromide .	$CH_2Br.CH_2.CH_2.CH_2.CHBr.CH_3$	1·92	—
Two molecules of methyl bromide		0·3	—

The peculiarities of the six-hour figures are attributed to the presence of zinc oxide in the zinc dust. Here again the yield in the reaction between atoms in the α-position to each other far exceeds that of those in the γ-position.

Arguments based upon the formation of cyclic compounds are apt to be fallacious in this special branch of the subject; for in most cases all that we can do is to measure the stability of the ring after it has been formed, which is a very different thing from measuring the amount of energy required to form it. In the case of maleic and fumaric acid, for example, we can determine the amount of energy necessary to convert the unfavourably configured fumaric acid into the maleic form, which is more favourable to anhydride formation; we can then estimate the energy required to change the acid into the anhydride. Next, reversing the process, we can determine the stability of the anhydride ring, and the amount of energy liberated when maleic acid is transmuted into fumaric acid. We are enabled to do this by the fact that each of the intermediate compounds is a stable substance with which we can deal practically. But when we come to estimate the difference between (*a*) the amount of energy required to form a lactone from an acid whose atoms are arranged in space in a zig-zag

form, and (*b*) the amount of energy which the same operation will require after the atoms of the acid have been brought into a more or less cyclic configuration, we have no experimental method at our disposal. For the cyclic configuration, once formed, may be as unstable as the zig-zag one; we have no means of knowing whether it is or not; and in any case we cannot isolate the intermediate form. With the exception of Petrenko-Kritschenko, every one who has attacked the problem seems to have been confused by this; and yet it seems obvious that two operations are necessary in order to form a ring compound: (1) the chain of atoms must be brought into a cyclic configuration; (2) the ring must be formed by joining the ends of the chain. The energy required for each operation is independent of the amount required for the other.

For the present, the material at our disposal is too meagre to allow of any dogmatisation on the subject. All that we can safely say may be summed up in a few words. We do know that the five- and six-membered rings are more stable than those containing a greater or less number of atoms: it therefore seems probable that in the normal chain compounds those containing five and six carbon atoms *can be brought into* configurations more nearly cyclic than those containing less than five, if the amount of energy expended be the same in each case. But from this we must not deduce that such a cyclic arrangement of the atoms is immutable. On the contrary, such an assumption appears quite unwarranted; for when we consider the external influences which at any moment are brought to bear upon a molecule, it seems in the highest degree improbable that any arrangement of atoms could maintain a rigid configuration for an appreciable time.

§ II. *METHODS BY WHICH THE CONFIGURATION OF MOLECULES MAY BE DETERMINED WITHOUT THE AID OF OPTICAL ACTIVITY.*

We must now turn to the second division of the subject, and examine the evidence by means of which we are led to assign certain configurations to open-chain compounds. In the case

of the sugars, it will be remembered, this was done by utilising the optical properties of the substances; but when we come to deal with compounds which are not optically active, the problem becomes much more complicated. In most cases it is insoluble, as the means at our disposal are insufficient. Even when we can put forward certain views, it can be done only in the most tentative manner. It must therefore be understood that the results with which we shall deal in the remainder of this chapter are merely exceptional cases in which some particular property of the substances enables us to ascribe certain configurations to them as being the most probable.

In the first place, we may mention the deductions of Bruni[1] from the formation of solid solutions. In his view, two organic compounds of analogous structure will form a solid solution only if their configurations are similar. Now, he finds, for example, that when determining the molecular weight of maleic and fumaric ester cryoscopically in succinic ester solution he obtains a normal value for maleic ester (149·5 to 164, calculated value 144); but with fumaric ester he gets the abnormal value of 797 to 914. From this he deduces that the configuration of the succinic acid molecule resembles that of fumaric acid rather than that of maleic acid. This implies that in succinic acid the carboxyl groups are averted from each other as far as possible, a question with which we shall deal later on from a different standpoint. In a similar manner, he concludes that stilbene resembles azobenzene in configuration. It appears probable that azo-benzene has the trans-configuration :—

$$\begin{array}{ll} C_6H_5-N & \\ \quad\;\;\, \| & \\ \quad\;\;\, N-C_6H_5 & \end{array}$$

so by analogy stilbene also should be a trans-compound :—

$$\begin{array}{l} C_6H_5-C-H \\ \qquad\;\;\, \| \\ \quad\;\; H-C-C_6H_5 \end{array}$$

---

[1] Bruni, *Ueber Feste Losungen*, *Ahren's Vortrags-sammlung*, VI.

Crotonic acid seems to stand in the same relation to butyric acid as fumaric acid does to succinic acid; while iso-crotonic acid behaves to butyric in the same way as maleic acid does to succinic acid. According to this, crotonic acid would have the fumaroid configuration, and the six compounds might be represented thus:—

$$\begin{array}{l} CH_3-CH-H \\ \qquad\quad | \\ \quad H-CH-COOH \end{array} \qquad \begin{array}{l} CH_3-C-H \\ \qquad\quad \| \\ \quad H-C-COOH \end{array} \qquad \begin{array}{l} H-C-CH_3 \\ \quad\ \ \| \\ H-C-COOH \end{array}$$

Butyric acid. Crotonic acid. Isocrotonic acid.

$$\begin{array}{l} COOH-CH-H \\ \qquad\qquad | \\ \qquad H-CH-COOH \end{array} \qquad \begin{array}{l} COOH-C-H \\ \qquad\qquad \| \\ \qquad H-C-COOH \end{array} \qquad \begin{array}{l} H-C-COOH \\ \quad\ \ \| \\ H-C-COOH \end{array}$$

Succinic acid. Fumaric acid. Maleic acid.

The configuration of phenyl-propionic acid was deduced in a similar way from the fact that it forms a solid solution with cinnamic acid of m.p. 133° C., but none with the allo-cinnamic of m.p. 69° C. Since the latter is supposed to be the maleinoid form, phenyl-propionic should be similar to a fumaroid derivative in configuration. Other instances are known, but it is not necessary to describe them in detail.

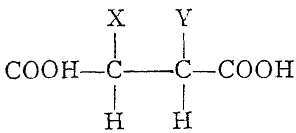
We have already shown the significance of the dissociation constants of acids in the problem of chain configuration: we may now give an example of their application to the present inquiry. If we take an ordinary monobasic aliphatic acid and determine the dissociation constants of it and its alkyl derivatives, we find that the more alkyl groups we introduce into the molecule the more we depress the dissociation constant. For example, the acetic acid series gives the following figures:—

		$K \times 10^2$
Formic acid	$H.COOH$	0 021
Acetic acid	$CH_3.COOH$	0·0018
Propionic acid	$CH_3.CH_2.COOH$	0·0013
Isobutyric acid	$(CH_3)_2.CH.COOH$	0·0014
Trimethylacetic acid	$(CH_3)_3.C.COOH$	0·000978

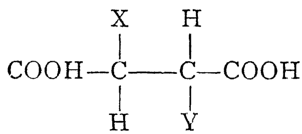
The same influence holds good in the malonic acid series also, as Walker's results[1] show :—

		$K \times 10^5$
Malonic acid	$CH_2.(COOH)_2$	0·158
Methyl-malonic acid . . .	$CH_3.CH.(COOH)_2$ . . .	0·086
Dimethyl-malonic acid . .	$(CH_3)_2.C.(COOH)_2$ . . .	0·076

When, however, we turn to the succinic acid series, the same rule does not appear to hold. It should be pointed out that the disubstituted succinic acids, like the tartaric acids, can exist in different stereoisomeric forms, the configurations of which may be indicated by the formulæ :—



Anti-form.



Para-form.

The dissociation constants for various substituted succinic acids, determined partly by Walden,[2] and later, with purer substances, by Bone and Sprankling,[3] are as follows :—

	K (Walden)	K (Bone and Sprankling)
Succinic acid	0·0068	
Isopropyl-succinic acid	0·0075	
Ethyl-succinic acid	0 0085	
Methyl-succinic acid	0·0086	0·00854
Isobutyl-succinic acid	0·0088	
Propyl-succinic acid	0·0091	
Allyl-succinic acid	0·0109	
Dimethyl-succinic acid (para) . .	0·0191	0·0196

[1] Walker, *Trans.*, **61**, 696 (1892).
[2] Walden, *Zeit. physikal. Chem.*, **8**, 433 (1891)
[3] Bone and Sprankling, *Trans.*, **75**, 839 (1899).

	K (Walden)	K (Bone and Sprankling)
Dimethyl-succinic acid (anti) . . .	0·0123	0·01235
Ethyl-methyl-succinic acid (para) .	0·0207	
" " " " (anti) . .	0·0201	
Trimethyl-succinic acid	0·0307	0·0321
Propyl-dimethyl-succinic acid . .	0·0551	
Ethyl-dimethyl-succinic acid . .	0·0556	
Tetramethyl-succinic acid	0·0314	

From these figures it is evident that the substitution in this case has had an effect opposite to the usual one, for it has raised the conductivity instead of decreasing it. Now, an increase in the conductivity of a dibasic acid generally implies that the carboxyl groups are being brought into closer proximity to one another. For instance, the conductivity of phthalic acid is greater than that of isophthalic acid, and maleic acid has a greater affinity constant than fumaric acid :—

	$K \times 10^{5}$
Phthalic acid	0·121
Isophthalic acid	0·029
Maleic acid	1·17
Fumaric acid	0·093

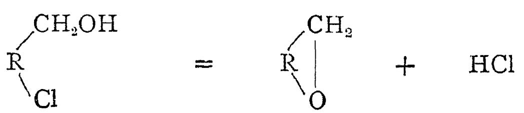
It appears probable that the effect of substitution in the case of the succinic series has been to force the carboxyl groups nearer to one another than they lie in the simple substance. Now, from Bruni's results we are justified in treating succinic acid as having the fumaroid configuration, so that its two carboxyl radicals may be supposed to lie as remote from each other as is possible within the molecule. Substitution evidently brings about a change into the maleinoid form; but while in the case of unsaturated compounds this change takes place in one step, in the case of the saturated substances, owing to the free rotation of the carbon atoms around their axes, the process is a very gradual one, each new group introduced into the molecule pushing the carboxyls a little nearer together. Thus, from

the affinity constants we can gain a certain amount of information with regard to the configuration of these acids.

Evans[1] endeavoured to determine the configurations of various chlorohydrins by comparing the velocities with which hydrochloric acid was eliminated from them under identical conditions. The method employed by him was as follows. Equimolecular quantities of the monochlorohydrin and caustic potash in very dilute solution were mixed together, and the amount of potassium chloride formed was estimated from time to time. On account of secondary reactions, the coefficients calculated from the equation of a bimolecular reaction were more or less variable; and he was therefore forced to have recourse to extrapolation in order to obtain more accurate results. By this means he calculated the following results :—

Velocity constant.	24·5° C.	34° C.	43·6° C.
$CH_2Cl.CH_2OH$	0·0068	0·0193	0·0523
$CH_3.CHCl.CH_2OH$	0·049	0·147	0·031
$(CH_3)_2:CCl.CH_2OH$	1·73	4·70	11·00
$(CH_3)_2:CCl.CH(CH_3)OH$.	1·93	5·00	9·40
$CH_2Cl.CH(OH).CH_2Cl$ . .	0·76	2·27	6·70
$CH_2Cl.CHCl.CH_2OH$ . . .	0·32	0·54	0·96
$CH_2Cl.CH_2.CH_2OH$ . . .	Practically undecomposed.		

These results he interprets in the following manner. He starts from the assumption that the speed of the reaction :—



is chiefly influenced by the distance which separates the chlorine atom from the hydroxyl group. The stereochemical formulæ of the chlorohydrins must therefore be brought into agreement with the velocities found by him. In this way he arrives at the configurations which we shall now describe A

[1] Evans, *Zeit. physikal. Chem.*, 7, 337 (1891)

plane passing through the centres of gravity of all the carbon atoms in the chain (which are represented by tetrahedra) is called by Evans a *Principal Plane.* In ethylene chloro-hydrin the chlorine atom and the hydroxyl group lie in one of these principal planes, but diametrically opposite to one another in the molecule, as shown in the figure :—

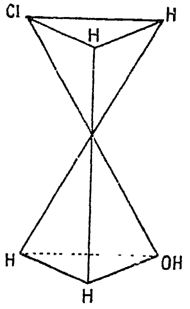


FIG. 50.

In monomethyl-ethylene chlorohydrin the two groups no longer lie in a principal plane, but are placed as in the figure below :—

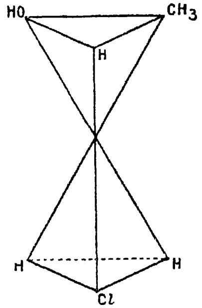


FIG. 51.

For dimethyl-ethylene chlorohydrin, the configuration, in which the chlorine and hydroxyl lie in a principal plane, is selected by Evans :—

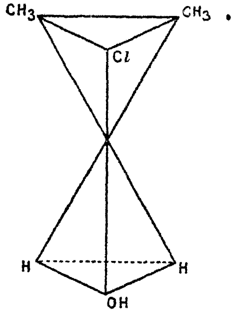


FIG. 52.

There are two possible configurations for trimethyl-ethylene chlorohydrin :—

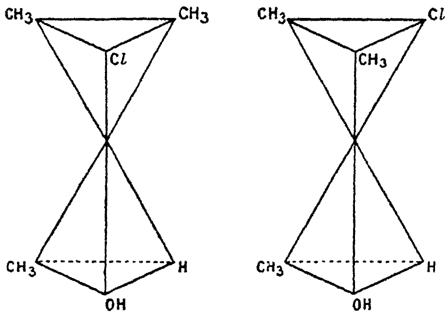


FIG. 53.

In trimethylene chlorohydrin the chlorine atom and the hydroxyl group again lie in a principal plane :—

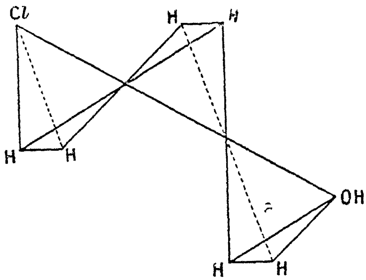


FIG. 54.

As regards the two dichlorohydrins, Evan ascribes to the symmetrical one the configuration :—

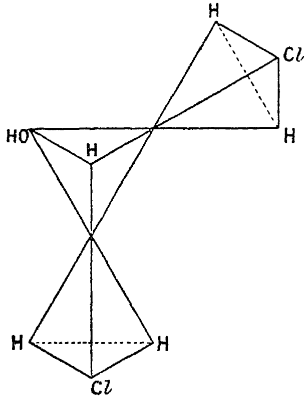


FIG. 55.

and to the unsymmetrical one the following configuration :—

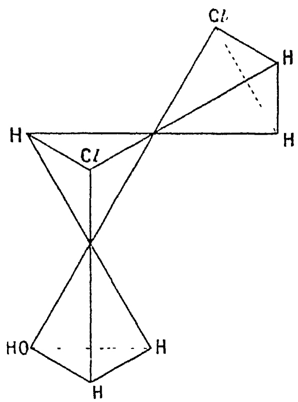


FIG. 56.

Now, when we examine these figures, it is evident that the relative distances between the chlorine atom and the hydroxyl

radical may be expressed by the length of the heavy line in the four following diagrams :—

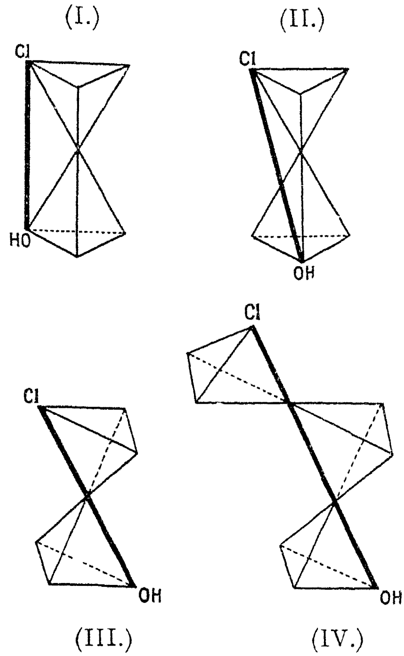


FIG. 57.

A comparison with the experimental results shows that if we attribute configuration (I.) to dimethyl-ethylene chlorohydrin, (II.) to monomethyl-ethylene chlorohydrin, α-dichlorohydrin, and β-dichlorohydrin, (III.) to ethylene chlorohydrin, and (IV.) to trimethylene chlorohydrin, we shall obtain a series of configurations which agree fairly well with the experimental results. Trimethyl-ethylene chlorohydrin may be either (I.) or (II.). It should be observed that in β-dichlorohydrin only one of the chlorine atoms is active.

It is very curious that Evans and Petrenko-Kritschenko, starting from kindred results, should arrive at conclusions

which are diametrically opposed to each other. Evans finds in his experiments a conclusive proof of the semi-cyclic arrangement of three carbon atoms; while Petrenko-Kritschenko, arguing from very similar data, denies its existence.

We have now completed our review of the problem of the determination of the configuration compounds which are not optically active; and it has been made evident that, when deprived of the aid of the polariscope, we are unable to make any great progress. It is possible that the question might be attacked with greater chance of success by working at very low temperatures; as in that case, judging by analogy, at least, we might hope to render more stable the configurations with which we have to deal. Until some such method is employed, it appears that the problem is unlikely to be solved.

CHAPTER V.

THE SPACE FORMULA OF BENZENE.

It would be impossible in the compass of this chapter to give anything like a complete account of the history of the space formula of benzene; all that can be done is to summarise the salient points of the more-important formulæ which have been proposed at one time or another, and to point out where theory and experiment agree and where they differ. In the first place it will be necessary to review the requirements which a space formula for benzene must fulfil; those properties of the compound which are not directly concerned in its space relations will not be mentioned.

It need scarcely be pointed out that the only reason for constructing a space formula for any compound lies in the hope that in such a formula the properties and reactions of the substance in question may find a better expression than could be given by an ordinary structure formula.

§ I. *THE POSSIBILITY OF PRODUCING MOLECULAR ASYMMETRY BY SUBSTITUTION.*

In considering the possible space formulæ for benzene, classification of some sort will be necessary: and the simplest method of division seems to be to class the various formulæ according to whether the carbon atoms lie in one plane or not. This question arose very early in the history of stereochemistry, and as many attempts were made to settle which of these configurations was the actual one, a short account of these researches will be given here.

It is obvious that if all the hydrogen atoms in benzene lie in one plane, optical activity could not be shown by benzene compounds, since there could be no enantiomorphism, even in the case of benzene substitution products. On the other hand, if the prism or any similar formula were correct, an ortho-disubstitution product should be optically active. Le Bel[1] endeavoured to isolate active *o*-toluidine: Lewkowitsch[2] made the attempt with two methyl-salicylic acids; Victor Meyer and Lühn[3] used nitro- and formyl-thymotic acids; while H. O. Jones and Kewley[4] attempted to resolve di- and tri-substituted amido-benzene derivatives by means of *d*-camphorsulphonic acid. All were unsuccessful, and it has been concluded that no asymmetry can be produced even when all the groups attached to the benzene nucleus are different from one another Apparently the only possible explanation for this is to assume that all the hydrogen atoms lie in one plane.

There is, however, another side to the question. According to Fischer,[5] "in order to bring about chemical action, enzyme and glucoside must fit one another as a key is fitted to a lock;" and Winther[6] has made a similar statement with regard to resolution by means of active bases. Now, in the case of aliphatic compounds, all the carbon atoms may be considered either as lying in one plane or as capable of being brought into one plane without any breakdown in the internal structure of the molecule. If, on the other hand, the carbon atoms in the benzene molecule do not lie in one plane, and cannot be brought into a plane by any simple movement among themselves, it is quite possible that such a difference from ordinary structure would be sufficient to defeat any ordinary method of splitting; and that a separation of a benzene derivative into

[1] Le Bel, *Bull. Soc. chim.*, [2] **38**, 98 (1882).

[2] Lewkowitsch, *Trans.*, **53**, 791 (1888); compare *Ber*, **16**, 1576 (1883)

[3] V. Meyer and Luhn, *Ber.*, **28**, 2795 (1895).

[4] Jones and Kewley, *Proc. Camb. Phil. Soc.*, **12**, 122 (1904).

[5] Fischer, *Ber.*, **27**, 2992 (1894).

[6] Winther, *ibid*, **28**, 3000 (1895).

two optical isomers would require the employment of some hitherto undevised method for its accomplishment.

Again, it is quite possible to imagine that the carbon atoms of the benzene molecule are in a state of vibration, such that at one moment their centres lie in a plane, while the next moment some of them move out of this plane and take up new positions in space, from which they may again return into the plane containing the others. Such a vibratory system would be three-dimensional, and yet no asymmetrical substitution could render it optically active: for if a spacially asymmetrical substance were produced, its vibration would carry it through the plane phase, in which it is inactive, into the opposite enantiomorphous form; and the resulting substance would be unresolvable by any means at present at our disposal.

Since the question appears to be still an open one, the following pages will deal with both types of benzene space formulae.

§ II. *THE REQUIREMENTS OF A SPACE FORMULA FOR BENZENE.*

In any space formula representing the benzene molecule the following facts must be accounted for:—

(1). The equal value of the six carbon atoms.

(2). The equal value of the six hydrogen atoms.

(3). The existence of one mono-substitution derivative, three di-substitution derivatives, etc.

(4). The existence of di-, tetra-, and hexa-hydro-derivatives.

(5). The relation between hydrogen atoms in the ortho- and para-positions; and that between two hydrogen atoms in the meta-position to one another.

(6). That six carbon atoms are necessary to form the "benzene nucleus."

(7). The distinction between benzenoid and paraffinoid derivatives.

To these a further requirement might be added, if the views of Pasteur and van't Hoff be adopted:—

(8). The molecule must have a plane of symmetry.

§ III. *DISCUSSION OF BENZENE SPACE FORMULÆ.*

It will be found simplest to arrange the formulæ in the following order :—

(1). Those in which the centres of all the carbon atoms lie in one plane.

(2). Those formulæ in which the centres of carbon atoms lie in two parallel planes.

1. Formulæ in which the Centres of all the Carbon Atoms lie in One Plane.—The first of these space formulæ, which has recently been adopted by Graebe,[1] is produced simply by

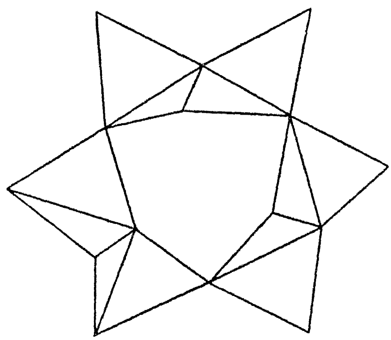


FIG. 58.

linking six tetrahedra together in the manner indicated in the ordinary Kekulé formula. It is evident that in this form the space formula suffers from exactly the same drawback as the plane formula, since the positions 1,2 and 1,6 are different, and hence two types of ortho-substituted compounds might be expected. By adopting Kekulé's vibration hypothesis, however, this difficulty can be avoided. For example, if it be supposed that the corners of the tetrahedra at the back of the model always remain in contact, while those in front vibrate alternately to right and left, a spacial representation of the Kekulé

[1] Graebe, *Ber.*, **35**, 526 (1902).

vibration formula will be obtained which has all the advantages of the plane formula, but no more.

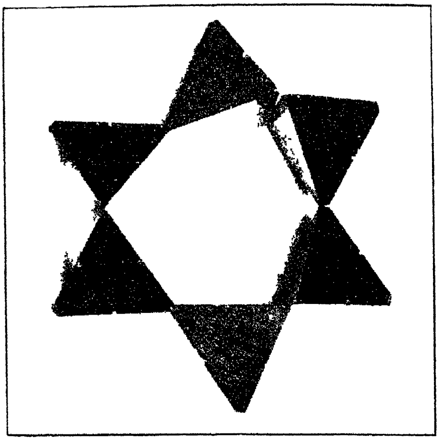


FIG. 59.

A somewhat similar formula was proposed by Wunderlich.[1]

A second type of space formula in which the centres of all the carbon atoms lie in one plane is that put forward by Marsh,[2] Baeyer,[3] Lohschmidt,[4] and Erlenmeyer junior.[5] A criticism of it by Thiele[6] cannot be summarised in this place, but his main objections may be mentioned. The model is constructed by laying six tetrahedra upon a plane hexagon. (See Figs. 60 and 61.)

The drawbacks of this formula far exceed any merits that it may have; the chief cases in which it is obviously in contradiction with our present knowledge are as follows :—

[1] Wunderlich, *Konfiguration organischer Moleküle*, p. 21.
[2] Marsh, *Phil. Mag.*, **26**, 426 (1888).
[3] Baeyer, *Annalen*, **245**, 123 (1888).
[4] Lohschmidt, *Monatsh.*, **11**, 28 (1890).
[5] Erlenmeyer junior, *Annalen*, **316**, 57 (1901).
[6] Thiele, *ibid.*, **319**, 136 (1901).

(1). The para-carbon atoms are situated with regard to one another exactly as the middle carbon atoms in succinic acid; so that terephthalic acid should give an anhydride with the same ease as succinic acid

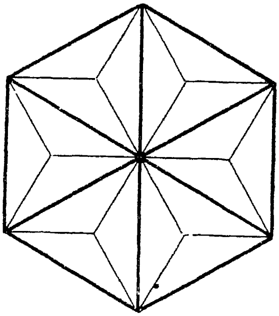


FIG. 60.

(2). Iso-phthalic acid also should give an anhydride.

(3). The acid $HO{-}\overset{(1)}{C}H_2{-}C_6H_4{-}\overset{(2)}{C}OOH$ would be analogous

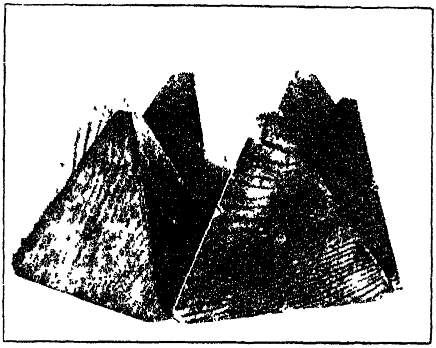
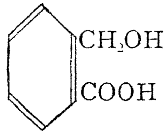
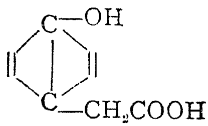


FIG. 61.

to γ-hydroxy-butyric acid, and should give a lactone. The same holds for p-hydroxy-phenylacetic acid.



CH_2—CH_2OH
$|$
CH_2—COOH



Yet a third formula of a similar type has been proposed by Knoevenagel,[1] but in it no assumption as to the form of the carbon atom is made. Knoevenagel makes the two following postulates :—

(1). The atoms, which have a certain mass, are in continual rapid motion within the molecule.

(2). The four valencies, or, rather, the four maxima of attraction of the carbon atom, are directed outwards from a point in directions parallel to lines joining the centre of a tetrahedron to its corners.

For the sake of the graphic representation the atoms may be supposed to be spheres whose centres lie in the plane of the paper ; the affinities holding the hydrogen atoms may be supposed to be directed upwards from this plane, and to be denoted by the dots in the centres of the circles, which represent the equators of the carbon atoms. The alternate atoms are supposed to revolve in different directions, one clockwise, the next counter-clockwise, as shown by the arrows in the figure. The drawback to this theory lies in the fact that though it evades the difficulty as to the possibility of two

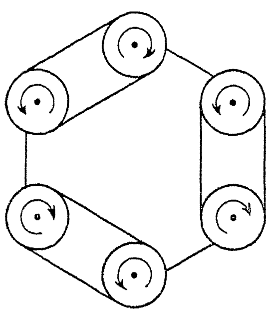


FIG. 62.

[1] Knoevenagel, *Ber.*, **36**, 2803 (1903).

ortho-disubstitution products, at the same time it introduces the possibility of a whole series of isomers, which would owe their existence to the differences in the directions in which the carbon atoms are supposed to rotate. Knoevenagel points this out himself, but considers that such isomers would be very difficult to detect. As an example of a case which may possibly be due to this cause, he quotes the fact that two benzophenones exists, and explains their difference by supposing that in the one case the two carbon atoms joined by the carbonyl group rotate in the same direction, while in the other isomer one is revolving clockwise and the other counter-clockwise.

Another formula which is included in this class was put forward by Werner,[1] and depends upon his conceptions of the carbon atom and the distribution of affinity, which have already been dealt with. If we suppose six atoms united in a plane ring, each atom will come within the radius of attraction of all the other five atoms, and its exit from the ring will be thus hindered. Since, in the formation of the benzene ring, each carbon atom expends the same amount of energy as its fellows, the static condition of the molecule will be that in which the carbon atoms, independent of their positions with regard to one another, are bound together by the greatest amount of affinity. In Fig. 63 the surfaces marked *a* represent the spots at which the hydrogen atoms are attached. They are therefore left out of account at present, as they exercise no influence upon the rest of the affinity.

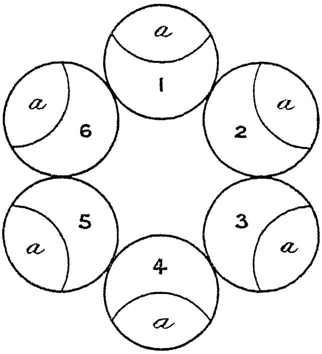


FIG. 63.

[1] Werner, *Beitrage zur Theorie der Affinitat und Valenz; Lehrbuch der Stereochemie*, p. 375.

It will simplify matters if we consider the action of the affinity of any carbon atom as resembling, to some extent, the radiation of light from a luminous source; thus, atom 1 may be supposed to be sending rays to the five other atoms. In such a case, the two atoms, 2 and 6, situated in the ortho-position to 1, will receive the greater portion of light, and furthermore, the amounts received by them will be equal. The atoms 3 and 5, on the other hand, will be shaded to some extent by the ortho-atoms, and so will receive but little illumination, while, in addition, such light as they do receive will be weakened and dispersed by the distance through which it has travelled. Finally, the atom 4 will receive its full amount of rays, but in its case also the light will be weakened, owing to the distance through which it has to travel.

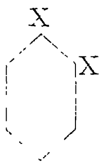
Exactly similar conditions will hold for the action of affinity if Werner's hypothesis be adopted. The greatest amounts of energy will be equally distributed between the two ortho-atoms; the atoms in the meta-position to one another will be bound together only by a small affinity, which will be further weakened by distance; while the para-atoms, though united by stronger affinities than meta-atoms, yet are so far apart that the affinity can exert nothing like its full force.

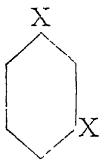
Only two important objections can be brought against the Werner formula. First, it does not show why six, and only six, carbon atoms are required to form a benzene nucleus and endow it with the aromatic character. If Werner's idea of the carbon atom be adopted, there seems to be no reason why a five-membered ring should not be as stable as a six-membered one, yet no compound of the type C_5H_5 is known which has such stability. And, secondly, it gives no clue to the relations found in benzene between the ortho- and para-positions, and among the meta-positions beyond the fact that the affinities between the atoms belonging to these two sets are not the same.

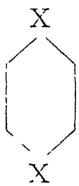
Baly, Edwards, and Stewart[1] have put forward a conception of the benzene molecule which accords with the chemical and

[1] Baly, Edwards and Stewart, *Trans.*, **89**, 514 (1906).

spectroscopic evidence known to us at the present time. No assumptions are made as to the form of the atoms or the directions in which their valencies act. It had been shown by Baly and Collie[1] that the absorption spectrum of benzene contains seven very similar and closely adjacent absorption bands; and these authors had pointed out that the formation of these seven bands can be accounted for by assuming that each band is due to a separate making and breaking of linking between pairs of carbon atoms of the ring. There are seven such makings and breakings possible, as can be seen from the following figures, the X's being attached to those atoms which are changing their linking :—


(1)


(2)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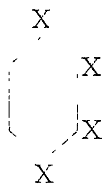
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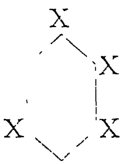
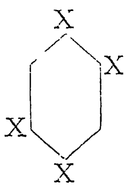
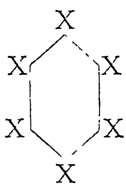
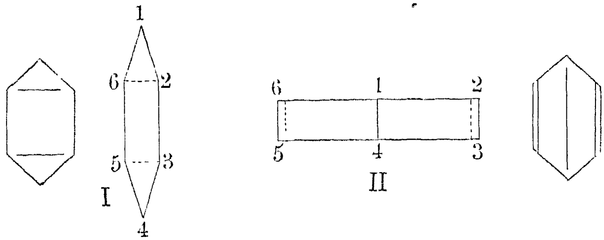

(5)


(6)


(7)

Now, in order to bring the seven phases into existence, it is necessary to assume the displacement of the carbon atoms of the ring. This can be done most simply by assuming that the vibration is similar to that produced in any elastic ring when it is disturbed. Thus it may be supposed that the ring pulsates in phases, of which (I) and (II.) are the extremes :—

[1] Baly and Collie, *Trans.*, **87**, 1332 (1905).



I II

Each carbon atom has residual affinity, and, consequently, when the system is in the condition represented by (I.), where the atoms 2 and 6 and the atoms 3 and 5 are brought close together, these residual affinities will produce linkings as shown by the dotted lines. The atoms 1 and 4, however, are far removed from one another and from the other atoms, and are therefore unsaturated. On the other hand, when the ring passes into the other form, (II.), then the three atoms 2, 1, and 6 come very close to the three atoms 3, 4, and 5 respectively, and linking between these pairs of atoms may take place. As the ring pulsates from (I.) to (II.), many of the seven phases of linkage-change described above will be obtained. For example, let us suppose that the ring has reached the form (II.). As it begins to open, the first break will occur between the atoms 1 and 4, followed by the breaking of the two subsidiary ortho-linkages 2:3 and 5:6. When the ring passes through the halfway stage, *i.e.* the circular form, the centric formula, corresponding to the seventh phase, will be produced. In this way the phases 1, 2, 3, 6, and 7 can be obtained; 4 and 5 would be the result of interference with the described motions by outside influences, such as collisions between molecules.

This formula accounts for many of the properties of benzene which are not easy to understand by the aid of the ordinary formulæ. For instance, Baly and Ewbank[1] have shown that phenol possesses keto-enol tautomerism; and it is evident that when the ring assumes the form (II.), the hydrogen of the

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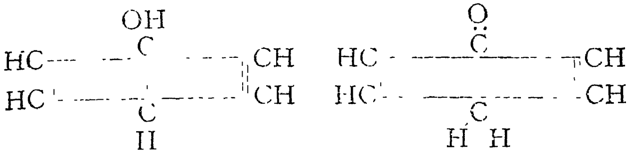
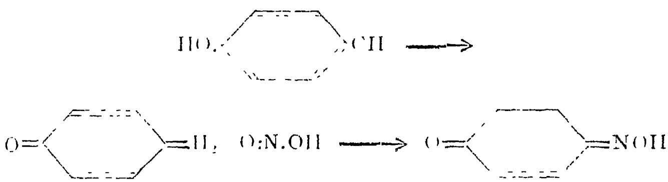
[1] Baly and Ewbank, *Trans.*, **87**, 1347 (1905).

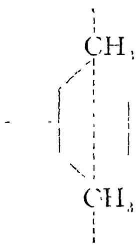
hydroxyl group will be in very close proximity to the $-CH=$ in the para-position. Wandering may thus easily occur.



This makes clear the mechanism of the action of nitrous acid upon phenol.

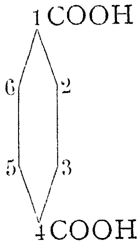


Baly and Ewbank have shown that the internal motions of the di-substituted benzene ring are less disturbed by para- than by ortho-substitution. This fact also is accounted for on the pulsating ring theory, for in *p*-xylene the vibrations of the ring would occur along the lines of symmetry of the molecule, and would not be much interfered with by the masses of the substituents.



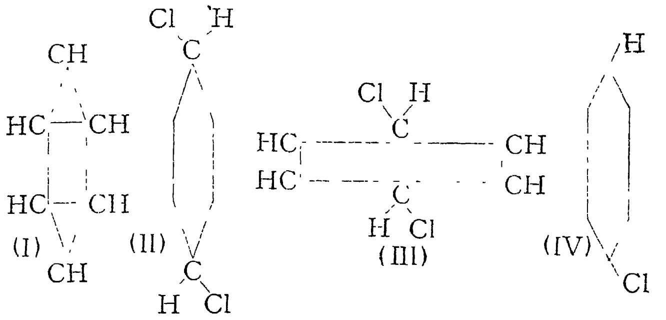
In the case of ortho-substitution, however, the unsymmetrical loading of the ring would make the vibrations much more complicated.

The same explanation can be applied to the reduction of the phthalic acids. In terephthalic acid, the vibration will not be disturbed by the substituents in the para-position; and the acid will exist to some extent in the following form :—

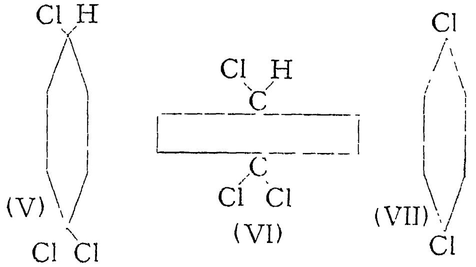


In that phase, the carbon atoms 1 and 4, being far removed from the other atoms of the ring, are unsaturated, with the result that they will each take up a hydrogen atom with ease, forming $\Delta^{2,5}$ dihydro-terephthalic acid. In the case of iso-phthalic acid, however, the ring's vibrations are greatly interfered with by the meta-substitution, so that it is doubtful if any of the carbon atoms in the ring reach the extreme phase of unsaturation. Isophthalic acid is therefore only reducible with considerable difficulty, tetra-hydro-acids being formed.

When benzene is chlorinated, the reaction-product is the *p*-dichloro-compound, the ortho-compound being only produced in small quantity. If we suppose the benzene ring to be in form (I.), the two carbon atoms at the ends of the ellipse will be unsaturated, as in the last case; and when the chlorine is brought into their reaction sphere, each carbon atom will take up an atom of chlorine. The result will be the formation of the compound (II.). When the opposite extreme of the vibration is reached, as in (III.), a molecule of hydrogen chloride will be eliminated, giving chlorobenzene. When the first shape is again reached, the same process will be gone through again as shown in the other figures, *p*-dichlorobenzene being the end-product :—



(I) (II) (III) (IV)



(V) (VI) (VII)

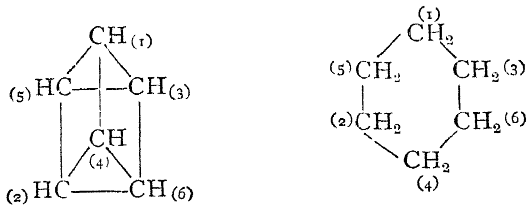
It has been shown by Baly and Collie[1] that in nitrobenzene the motions of the ring are in some way held up: this is probably due to the unsaturation of the nitro-group. At any rate, in the nitro-benzenes the true benzenoid vibration is absent; and this explains why the nitration of halogen benzenes tends to make the halogen atom more labile than it usually is in benzene compounds; for when the vibrations of the ring are damped down, the compound will tend to become more like an ordinary fatty derivative.

2. Formulæ in which the Centres of the Carbon Atoms lie in Two Parallel Planes.—The earliest space formula for benzene was proposed by Havrez in his *Principes de la chimie unitaire* in 1866. In his formula, the carbon atoms were arranged in two parallel planes. His ideas are of historical interest only.

---

[1] Baly and Collie, *Trans.*, **87**, 1332 (1905).

The first of this class which need be described is the Ladenburg Prism Formula.[1] In it, the six carbon atoms lie in two sets of three, each three being placed at the angles of an equilateral triangle, and the two triangles lying parallel to one another in space :—



The ortho-, meta-, and para-positions may be recognised from the numbers attached to the carbon atoms. They are the only ones which agree with the isomerism relations of benzene. Now, on reduction, it is evident that these relations are not maintained, for in hexahydrobenzene two of the benzene para-positions have been converted into ortho-positions. Also, meta- and para-dicarboxylic acids should give anhydrides more easily than the ortho-dicarboxylic acid. Hence the Ladenburg formula, though in some respects interesting, has but little practical value.

A second formula of the same class has been put forward by three different authors: Vaubel,[2] Marsh,[3] and Chicandard.[4] Since Vaubel appears to have elaborated it to the greatest extent, it will be sufficient to describe his model.

According to his view, the benzene nucleus is made up of six carbon atoms of tetrahedral form, so arranged that each atom is joined by the edges of the tetrahedron to two other atoms, while the atoms themselves lie alternately above and

---

[1] Ladenburg, *Ber.*, **2**, 140 (1869); *Theorie der aromatischen Verbindungen*, Brunswick, 1876.

[2] Vaubel, *J. pr. Chem.*, [2] **44**, 137 (1891).

[3] Marsh, *Phil. Mag.*, **26**, 426 (1888).

[4] Chicandard, *Compt. rend. de l'Assoc. franc. pour l'Avancem. des Sciences*, **1900**, 480.

below the plane formed by their bases. In other words, this configuration differs from Baeyer's in that instead of all the hydrogen atoms lying in one plane, they lie alternately above and below it.

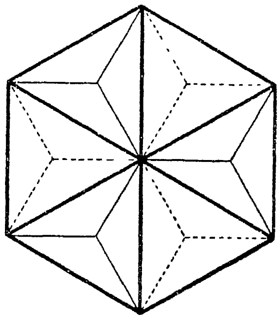


FIG. 64.

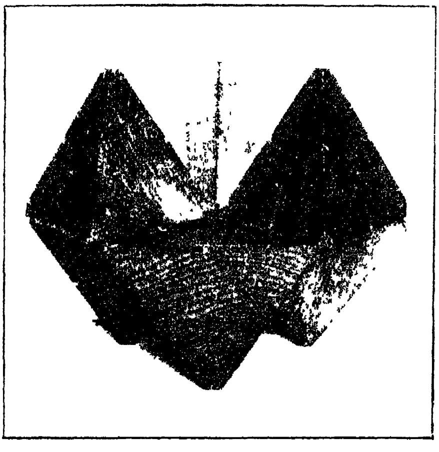


FIG. 65.

The drawbacks to this configuration are obvious.—

1. Isophthalic acid would give an anhydride more easily than phthalic acid.

2. Resorcinol ought to give a methylene ether.
3. There would be no reason for the V. Meyer Esterification Law.*
4. Ortho- and meta-disubstitution should yield enantiomorphism.

To meet the first objection, Vaubel supposes that in isophthalic acid there is a special configuration which prevents anhydride formation. If the rest of the molecule be represented by a straight line, his explanation may be expressed as follows:—

$$\begin{array}{ccc} \mathrm{HO{-}C{:}O} & \qquad & \mathrm{O{:}C{-}OH} \\ | & & | \\ \hline \end{array}$$

so that instead of the hydroxyl groups coming into contact with one another, only the oxygen atoms of the carbonyl groups could collide. His explanation why no enantiomorphism is shown in the cases mentioned, is founded on the assumption that the tetrahedra are in a state of vibration about the axes furnished by their outer edges, *i.e.* those edges which make up the hexagonal figure. But this assumption involves a wandering of any substituent group from one valency of the carbon atom to another, and up to the present such an idea seems to have found little favour.

Another formula in this class † is due to Sachse.[1] (See Figs. 66 and 67.) To a certain extent, this configuration is better than any that have already been mentioned. It contains meta-atoms in the same plane, ortho- and para- in separate planes; it may be applied to some higher aromatic series; and it illustrates well the difference between aromatic and fatty compounds. On the other hand, much may be said against it. It is evident that a six-membered ring thus constituted will be one of the most stable compounds which it is possible to conceive; there will be no possibility of any movement whatever within the molecule, and the formula represents simply a rigid body.

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* See Chapter I. of this section.

† Directions for the construction of a model are given in Appendix B.

[1] Sachse, *Ber.*, **21**, 2530 (1888).

Such a conception of any molecule does not at the present time seem to be in harmony with our general ideas as to the

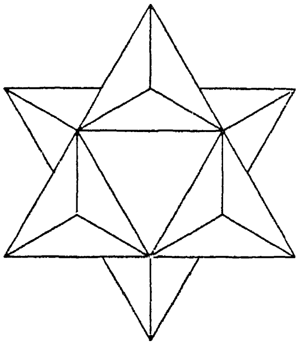


FIG. 66.

FIG. 67.

behaviour of atoms. Further, Sachse supposes a kind of union between carbon atoms which could not exist in any other compound, and which leads to the saturation of the affinities of three

carbon atoms at one point. Apart altogether from such purely theoretical objections, moreover, there are certain practical ones which appear to be insurmountable.

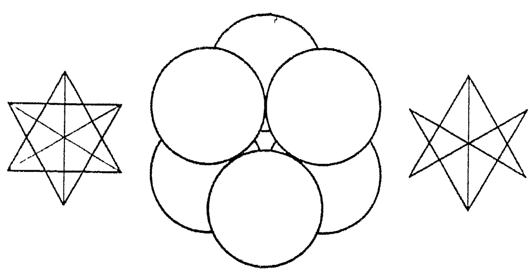
1. Isophthalic and phthalic acids should give anhydrides with almost equal ease.

2. Resorcinol should give a methylene ether.

3. Enantiomorphism would be inevitable in some substitution products, since there is no possible vibration by which it could be avoided.

By adopting Werner's conception of the carbon atom, and applying it to atoms arranged like those in the Vaubel and Sachse models, Bloch[1] has produced a space formula for benzene which seems to unite the advantages of both the others without their drawbacks; and by assuming certain vibrations, according to him, it is possible to bring it into line with nearly all the older formulæ, as the following figures show. To a certain extent, however, Bloch's model is merely a repetition of Collie's, which was proposed six years earlier.

Owing to the differences in the arrangement of the atoms in space, Bloch's formula shows a complete variation from Werner's when the strengths of the affinities between the various atoms are considered, *e.g.* in Werner's model the affinities between atoms in the meta-position to one another are small, which is not the case in Bloch's formula.



Ladenburg. Thomsen.

[1] Bloch, *Alfred Werner's Theorie des Kohlenstoffatoms*, p. 60

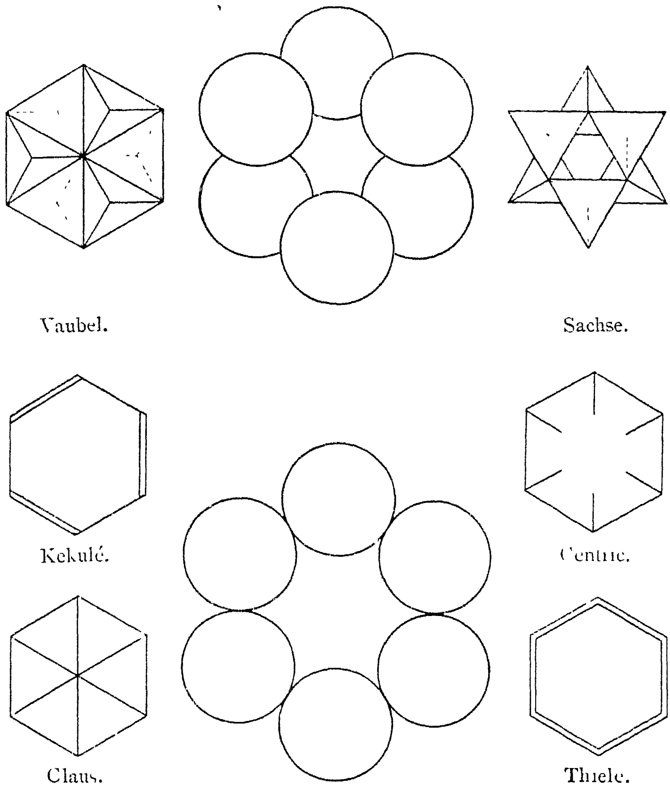


FIG. 68.

Barlow and Pope,[1] basing their hypothesis on the crystalline form of benzene, and employing a method of scission similar to that previously proposed by Stewart in the case of the transmutation of geometrical isomers, have suggested a space formula for benzene resembling the top diagram in Fig. 68. Their formula is very interesting from the point of view of crystallography, but appears to have little or no connection with the chemical character of the

[1] Barlow and Pope, *Trans.*, **89**, 1675 (1906)

benzene molecule. By its rigid construction it is allied more closely to the older types of space formulæ than to those vibrating systems favoured by modern views.

Herrmann[1] proposed the following space formula. The six carbon atoms are placed at the corners of a regular octahedron; the hydrogen atoms are situated at the angles of a regular hexagon, which lies on a median plane of a hexahedron, the middle points of whose sides correspond to the angles of the octahedron.

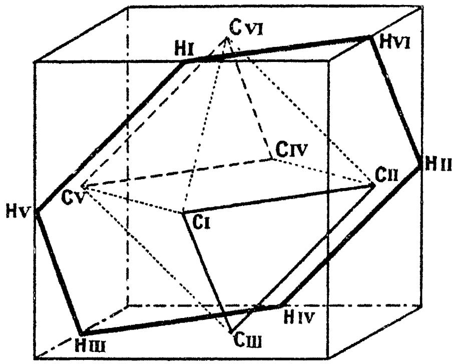


FIG. 69.

The projection of the positions of the carbon atoms upon the plane in which lie the hydrogen atoms gives—

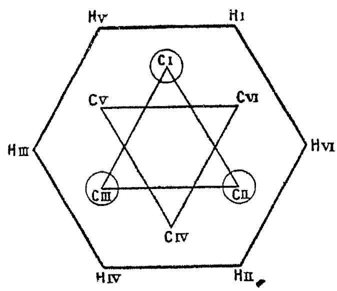


FIG. 70.

[1] Herrmann, *Ber.*, **21**, 1949 (1888).

in which the carbon atoms inside circles lie under, the others above, the plane.

When we consider two ortho- or meta-substitution products, in which the substituting groups are different from one another (*e.g.* as in *o*-toluidine), it is evident that there will be asymmetry in the molecule, and enantiomorphism should be the result.

Konig[1] has put forward the following view. The carbon atoms are arranged at the corners of a cube, as shown in the figure, two opposite corners being thus left vacant. The author points out that vibration would be possible in such a system, yielding first a rhomboid form, and finally a plane hexagonal arrangement. This formula is really a modification of Ladenburg's prism.

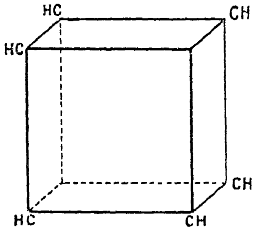


FIG. 71.

The last space formula for benzene with which we shall deal combines the good points of all the others with several advantages of its own. Owing to the introduction of a greater degree of vibration into its system, the formula suggested by Collie cannot be classed in either of the above divisions, as its phases include some in which the centres of the six carbon atoms lie in a plane, as well as other phases where three carbon atoms lie in a plane parallel to that containing the remaining three. Such a vibratory motion precludes any possibility of the existence of enantiomorphous benzene substitution products, and thus avoids the difficulties which arise from this source in those space formulæ for benzene in which all the carbon atoms are not in the same plane.

In Collie's space formula for benzene[2] the carbon atoms are arranged at the corners of an octahedron. No assumption is made as to the form of the carbon atoms, but here, for convenience, they are represented by tetrahedra. In order to fulfil the requirement that any one carbon atom must be linked

[1] Konig, *Chem Zeit.*, **29**, 30 (1905).
[2] Collie, *Trans.*, **71**, 1013 (1897).

to two others in a precisely similar manner, and that the connections are from two of the four symmetrically placed points of attraction which every carbon atom is supposed to possess, there is only one configuration possible (Figs. 72 and 73).

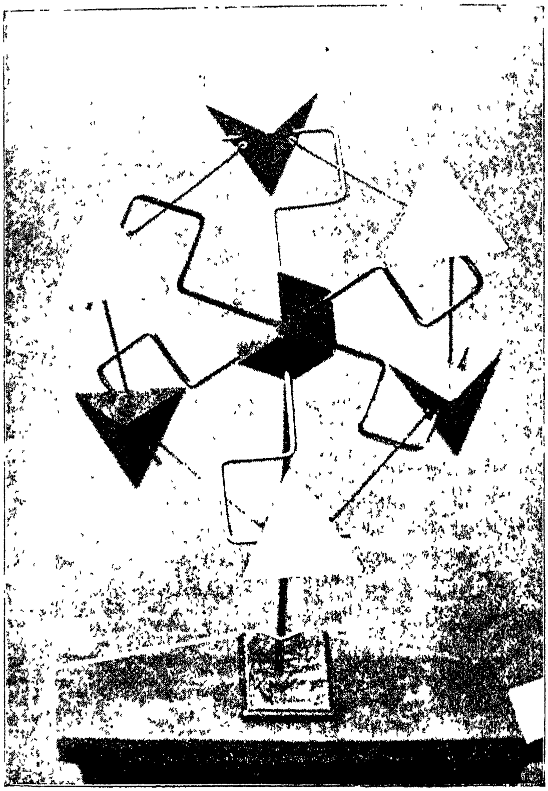


FIG. 72.—Front view.

Moreover, there is only one way in which six hydrogen atoms can be symmetrically arranged upon six of the remain-

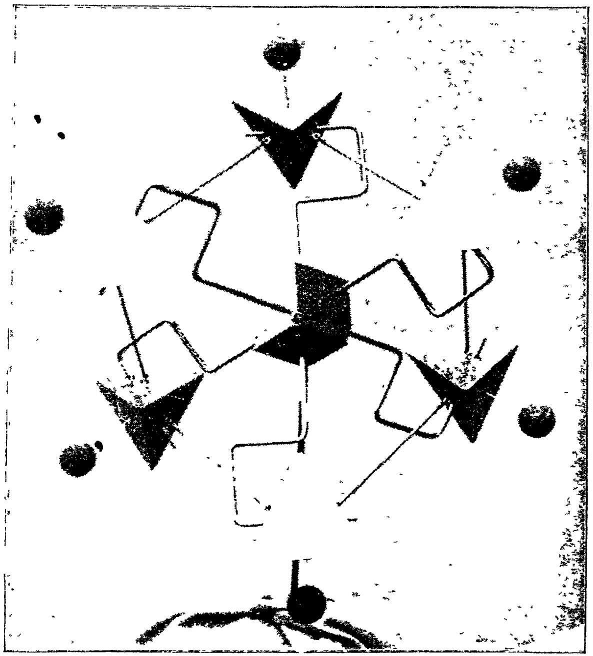


FIG. 74 —Symmetrical arrangement.

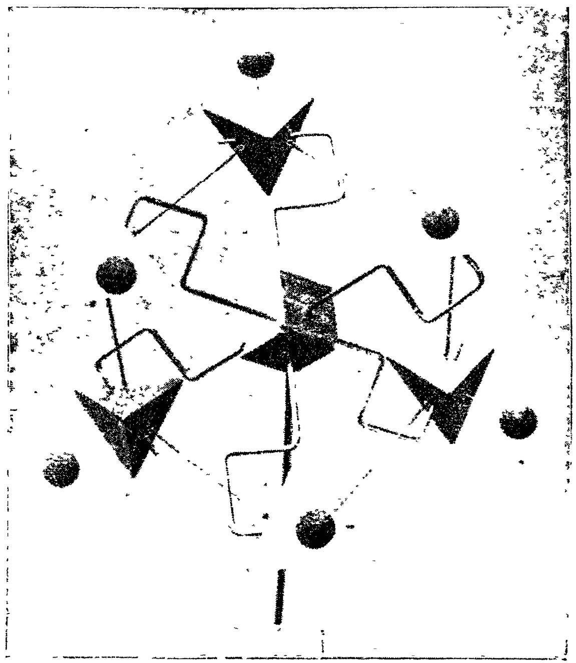


FIG. 75.—Unsymmetrical arrangement.

ing twelve points of attraction (Fig. 74). (Fig. 75 shows an unsymmetrical arrangement.) Movement in this system can take place in two ways :—

1. Movement of each tetrahedron about its centre.
2. Movement of each tetrahedron about the centre of gravity of the whole system.

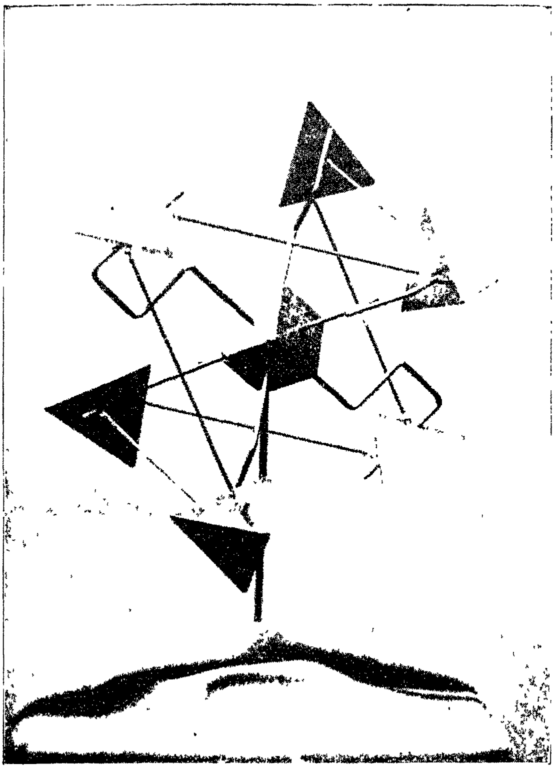


FIG. 73.—Side view.

In the first case, the simultaneous rotation of each tetrahedron about its centre (all tetrahedra being supposed to move in the same direction) would bring the combined hydrogen atoms toward the centre of the system in *two distinct sets*, these on the

1, 3, 5 carbon atoms and those on the 2, 4, 6 carbon atoms; so that when one set are towards the inside or near the centre of the system, the other three are outside and further away from the centre. In the second case, where the motion of the tetrahedra is a vibratory one about the centre of gravity of the system, any movement would alter the relative positions of the tetrahedra with regard to one another, bringing into play alternatively the six unsaturated points of attraction on these tetrahedra. (See Figs. 76, 77, and 78.)

In the first phase (see Fig. 76), an extreme position of the carbon atoms is shown. If any three carbon atoms be taken, for instance, 1, 2, 3, the position which 2 will tend to take up will be between 1 and 3; similarly, if 2, 3, 4 are taken, 3 will tend to take up a position between 2 and 4. Hence the carbon atom 2 will move to the right, and 3 will move in the opposite direction.

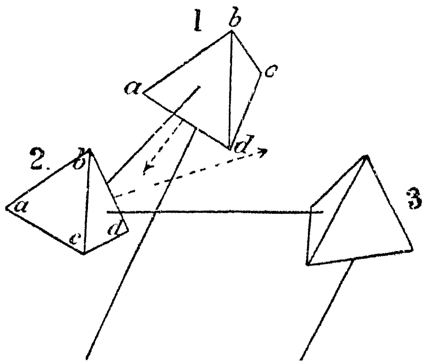


FIG. 79.

Figure 77 shows the intermediate phase between Fig. 76 and Fig. 78; but in this figure the view is taken sideways on a plane lying at right angles to that seen in Figs. 76 and 78.

As the carbon atom 1 in Fig. 79 moves in the direction indicated by the dotted line, and the carbon atom 2 in the direction of the other dotted line, a small rotation of the two carbon atoms about their centres will bring the vacant point of attraction on each into play for an instant, as shown in Fig. 80. The vacant points of attraction are on the faces *a*, *b*, *c* on both carbon atoms, the faces *a*, *b*, *d* on 1 and *a*, *c*, *d* on 2 being occupied by the hydrogen atoms. Thus for a moment there will be *almost* a double bond between the carbon atoms 1 and 2; and also between 3 and 4; 5 and 6.

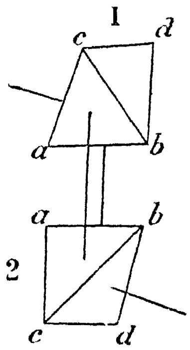
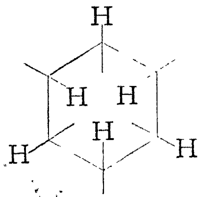


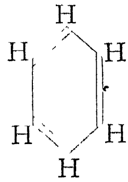
FIG. 80.

Continuing this movement when the six carbon atoms are all in one plane, as shown in Fig. 77, then, by the same rotation about their centres, either three or six vacant points of attraction would point toward the centre together; and finally, in the return movement from Fig. 78 to Fig. 76, owing to the twist given to the carbon atom 2, there would be, conversely, *almost* a double bond between it and the carbon atom 3; and also between 4 and 5; and 6 and 1.

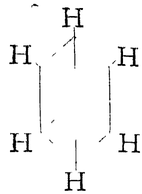
Taking the projections of these phases, we get the following:—



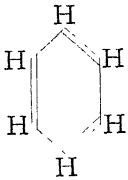
First phase



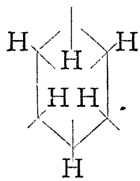
Kekulé's formula



Centric formula



Kekulé's formula



Last phase

This space formula for benzene, therefore, is in complete accord both with the Kekulé and the Centric formula; showing that they are mutually convertible into one another. It also shows how the supposed double linkages of the Kekulé formula shift between the carbon atoms, rendering the existence of two *o*-toluidines impossible. But it differs from both in that in two out of five configurations there are two distinct sets of hydrogen atoms. By means of this peculiarity of his formula, Collie has been able to give a possible explanation of the Crum Brown and Gibson Rule.[1]

The Collie formula differs from all those which have been already described in the ease with which it may be modified to suit various demands. For example, it is perfectly in accord with the formulæ of Ladenburg, Claus, or Dewar, or that of Baly, Edwards, and Stewart. This adaptability is not possessed in any degree by previous space formulæ, and it is this which makes the Collie formula superior to the others. At the same time, such modifications as need to be introduced in no way detract from the

[1] Crum Brown and Gibson, *Trans.*, **61**, 367 (1892).

other advantages which this formula possesses. The representation of the benzene molecule as a system in a state of continual vibration is only an advance along the road opened by Kekulé with his oscillation hypothesis: it certainly gives a truer representation of the chemical properties of benzene than do those stereo-formulæ in which the atoms are represented as firmly anchored to one another, or squeezed together so tightly that no movement of any kind is possible.

§ IV. *CONCLUSION.*

The objections brought against the older types of space formulæ show that any advances in this branch of the subject must follow the lead given by Kekulé when he adopted the idea of a system in vibration as the best representation of the benzene molecule. At the present day, the idea that benzene is one particular substance which can be represented at all times and under all conditions by the same rigid formula finds very few supporters among those who have studied the question thoroughly. It is becoming generally recognized that the benzene molecule is in a state of continual vibration, and that the only satisfactory space formula will be one which represents all the other formulæ as phases of its own motions, and which may even suggest the possibility of new phases as yet unrecognized. The main outlines of such a formula have been indicated by Collie; and it seems probable that any space-formulæ of benzene which may be proposed in future will agree with his in essentials.

CONCLUSION.

We have now completed a survey of the whole field of stereochemical research; and have shown the lines along which that research has travelled in the past. At this point it may be well to examine the results achieved, and from them, if possible, deduce the direction which future investigation will take.

Stereochemistry is a subject of comparatively recent growth. Barely a generation has elapsed since the publication of van't Hoff and Le Bel's first papers, from which the modern development of the subject may be said to take its rise; yet during that comparatively short space of time the matter has been studied so exhaustively that to-day not only do we know its outlines, but in many of its branches there seems little scope for doing more than amassing experimental data with a view to future generalizations.

The problems of optical activity, which first led to the introduction of spacial ideas into chemistry, seem now to be passing into a new stage, and to be treated more from the point of view of the physicist than from that of the pure chemist. Apart, however, from these mainly physical problems, there are others which require solution, and which seem most likely to be dealt with by chemical means. For example, the phenomena of racemisation, though they have been very closely studied by many workers, are not even yet completely clear to us. We know that certain active compounds may be racemised by heat, and we draw the deduction that during this process changes take place in the arrangements of the atoms in space; but we have no idea of the nature of this

rearrangement, whether it be caused by the atoms concerned splitting off from the rest of the molecule, into which they are subsequently assimilated in new positions; or whether the change is produced merely by the intramolecular vibration of the atoms increasing in amplitude until they fall into new positions from which they have no cause for return. The solution of such a question as this would lead to most valuable results, as it would enable us to decide, once for all, the problem of "directed" as opposed to "undirected" affinities; for the second view of racemisation is quite out of keeping with the idea of affinity being a series of forces acting in specific directions. At present, our knowledge favours the conception of affinity put forward by Werner, but a satisfactory solution is still lacking; and as this is one of the fundamental questions of stereochemistry, some definite answer to it is required.

The most important of all the problems connected with optical activity, from the point of view of stereochemistry, is that of the possibility of producing an optically active compound which contains no asymmetric carbon atom, but owes its activity to the asymmetry of its molecule alone. It may be said that such substances are already known, for in the case of the inosites there is no true structurally asymmetric carbon atom in the molecule. As was shown on a previous page, however, the activity of the inosite series may be traced to the presence of pseudo-asymmetric carbon atoms in their ring; so that this case is one requiring merely a slight modification of the definition in order that it may be included with the others. The real examples of asymmetric molecules which contain no asymmetric carbon atoms are to be found in compounds of the allylene series, such as:—

$$\begin{array}{ccccc} R_1 & & & & R_2 \\ & \diagdown & & \diagup & \\ & C & : C : & C & \\ & \diagup & & \diagdown & \\ R_3 & & & & R_4 \end{array}$$

for, as can be seen from the space formulæ below, the groups R_1, R_2, R_3, and R_4 lie at the corners of a tetrahedron; thus the molecule will be an asymmetrical body, and the two formulæ

are enantiomorphous. This case was foreseen by van't Hoff, and predicted by him in one of the early editions of his book on the arrangement of atoms in space.

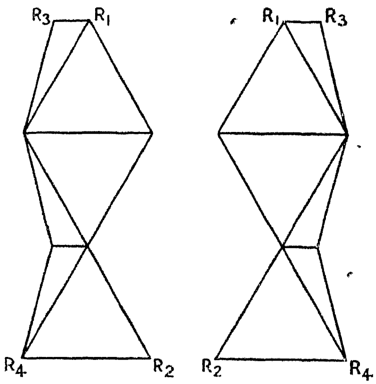
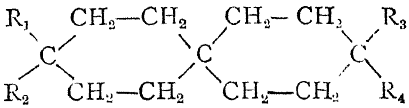


FIG. 81.

If the line R_1R_2 lies in the plane of the paper, the line R_3R_4 will be perpendicular to that plane. Instead of the double bonds we may interpose rings between the carbon atoms, without altering the asymmetry; for compounds of the type :—



would also occur in enantiomorphous forms. Several attempts[1] have been made to prepare substances of structure similar to the examples given, but up to the present nothing definite is known on the subject.

Inorganic chemistry has not yet reached a stage when stereoisomeric substances can be produced with the same ease

[1] Dimroth and Feuchter, *Ber.*, **36**, 2238 (1903); Marckwald and Meth, *Ber.*, **39**, 1171, 2035 (1906); Perkin and Pope, *Proc.*, **22**, 107 (1906).

as is shown in the carbon compounds; but among the salts of cobalt, platinum, and chromium, purely inorganic compounds have been isolated in stereoisomeric forms. It would be of very considerable interest if some of these could be prepared in an optically active condition. It would be easy to synthesise an asymmetric compound showing optical activity due to a carbon complex contained in it, but the crucial experiment would be one in which the compound contained no carbon atoms at all. If such a compound could be isolated, a new field would be opened up, greater in extent than that revealed by the discovery of those compounds which owed their activity to asymmetric atoms of nitrogen, sulphur, selenium, or tin.

The relations between vital action and molecular asymmetry have been studied by various workers in the past, and it seems probable that in the future, when more results have been attained, the connection between these two phenomena will be clearly defined. At the present time we are almost completely ignorant of this most important branch of the subject. The mechanism by which the living tissue builds up asymmetric substances is unknown to us, and we cannot even put forward a reasonable theory on the subject which is supported by any considerable experimental evidence. The work of Marckwald and McKenzie [1] seems to show that only those reactions which require a comparatively long interval of time for their accomplishment are capable of producing an asymmetric compound by direct synthesis; and it appears not improbable that time is one of the chief factors in the problem. This suggests that the processes of vital synthesis are slow in comparison with our laboratory reactions, and that during the long intervals through which these synthetic processes are going on in the living organism, various asymmetric forces in nature have a chance of exerting a more lasting and continuous influence upon the action. What these forces are cannot be dogmatically stated, as we know practically nothing on the subject; but it seems not improbable that the rotation of the earth, or

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[1] Marckwald and McKenzie, *Ber.*, **34**, 469 (1901).

terrestrial magnetism, or the motion of the earth around the sun, may have some effect.

Though our present theories suffice to explain the great majority of the cases of isomerism which have been observed up to the present time, a few instances are known which cannot be interpreted in accordance with these views; and since it is only by a study of exceptional cases that we can hope to advance into new fields, it may be well to direct attention to one or two examples of the kind.

In the first place, we may mention the cinnamic acids. It has long been known that three cinnamic acids exist, while current theories provide for two only. The matter was thus sufficiently complicated, but it has been rendered even more so by some recent work of Erlenmeyer junior,[1] by which he claims to have established the existence of a new type of isomerism. According to his views, the cinnamic acids from certain sources bear a strong resemblance to the racemic forms of compounds containing an asymmetric carbon atom, though differing from these in that the cinnamic acids show no optical activity. Erlenmeyer states that he has actually resolved cinnamic acid from storax into two stereoisomeric modifications; and for such a resolution our present theories give no explanation which can be considered really satisfactory. Marckwald and Meth[2] have contested the accuracy of Erlenmeyer's results, but the question cannot be said to be settled as yet. It seems desirable that some impartial person should repeat the work, with a view to putting it beyond any dispute. Apart altogether from this point, however, the case of the cinnamic acids deserves the most careful consideration.

An analogous case was observed by Lossen[3] in the hydroxamic acids. It has already been described in Chapter III., p. 216.

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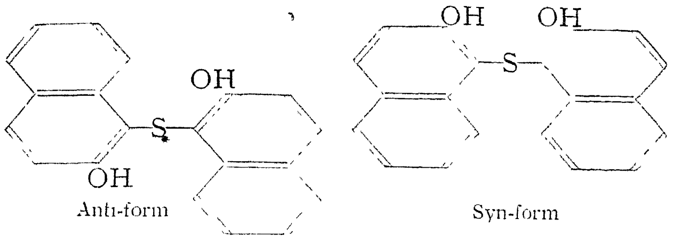
[1] Erlenmeyer junior and Arnold, *Annalen*, **337**, 329 (1905); Erlenmeyer junior, *Ber.*, **38**, 2562, 3496 (1905); *ibid.*, **39**, 788, 1570 (1906); Erlenmeyer junior, Barkow, and Herz, *Ber.*, **40**, 653 (1907).

[2] Marckwald and Meth, *ibid.*, **39**, 1176, 1966, 2598 (1906).

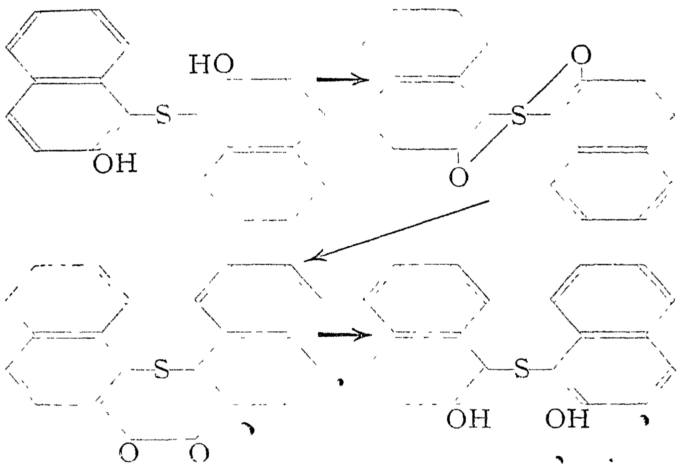
[3] Lossen, *Annalen*, **281**, 199 (1894); Lossen and Zanni, *Annalen*, **282**, 226 (1894); compare Werner, *Ber.*, **29**, 1150 (1896), and Subak, *ibid.*, 1153.

A very peculiar instance has been noted by Henriques[1] among the sulphur derivatives of β-naphthol. He obtained dihydroxy-dinaphthyl-sulphide in two forms, to which he ascribed the space formulæ :—



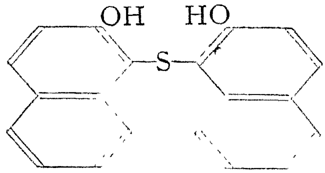
Anti-form Syn-form

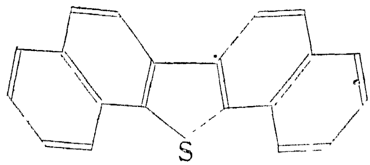
He found that the two compounds differed in melting-point, gave different acetyl derivatives, and one form could be converted into the other. The configurations were deduced from the behaviours of the two substances on oxidation. When the anti-compound is oxidised, the two oxygen atoms are united together, and the napthalene rings are thus pulled into the syn-configuration. On reducing this intermediate product, the syn-isomer is produced :—



[1] Henriques, *Ber.*, **27**, 2993 (1894).

Henriques found that from the syn-compound alone was it possible to split off both hydroxyl groups, thus forming a dinaphthalene-thiophene :—





It seems evident that this is a case which certainly cannot be explained on the ordinary stereochemical lines, and it is desirable that the point should be cleared up. It is not in accordance with our present views that a sulphur atom should introduce an element of rigidity into the molecule; and it seems more probable that the isomerism is not stereochemical in character. The question, however, is worthy of study.

Another anomalous case has been observed in the series of the dibenzylidene-succinic acids. Stobbe[1] states that these substances occur, as might be expected, in three isomeric forms corresponding to the space formulæ :—

$$\begin{array}{ccc} \mathrm{HOOC{-}C} & \text{———} & \mathrm{C{-}COOH} \\ \| & & \| \\ \mathrm{C_6H_5{-}C{-}H} & & \mathrm{H{-}C{-}C_6H_5} \end{array}$$

$$\begin{array}{ccc} \mathrm{HOOC{-}C} & \text{———} & \mathrm{C{-}COOH} \\ \| & & \| \\ \mathrm{C_6H_5{-}C{-}H} & & \mathrm{C_6H_5{-}C{-}H} \end{array}$$

$$\begin{array}{ccc} \mathrm{HOOC{-}C} & \text{———} & \mathrm{C{-}COOH} \\ \| & & \| \\ \mathrm{H{-}C{-}C_6H_5} & & \mathrm{C_6H_5{-}C{-}H} \end{array}$$

[1] Stobbe, *Verh. d. Ges. deut. Naturforsch. u. Aertzte*, Munich, **1899**, p 88.

Each of these has its characteristic anhydride, but there appears to be a fourth anhydride capable of existing, which can be changed into one of the three by exposing it to sunlight; and for the formation of this substance we have no explanation at present.

In addition to instances such as these, there are several cases known where isomerism has been suspected but is doubtful; and it appears desirable that an end should be put to this uncertainty. Cases in point are the anils, and isomerism in the compounds of the type *Nabc*. In this connection, it may be pointed out that one case has been overlooked in which stereoisomerism might be expected, namely, that of the trialkylamine or phosphine oxides. On the views at present accepted with regard to the configuration of pentavalent nitrogen compounds, and the analogy of similar compounds of phosphorus,[1] there seems no doubt that stereoisomerism should be shown by compounds of the type:—

From the study of such substances, many interesting data might be obtained; and it is to be hoped that attention may be directed to them in the near future.

Among the class of nitrogen stereoisomers, it seems strange that the azo-group does not appear to favour the occurrence of this type of isomerism. Janowski[2] described two trinitroazotoluenes and two *p*-azoxy-toluenes, but apparently this, and that of the azophenols described by Willstätter and Benz,[3] are the only cases known. A further investigation of this branch of the subject might yield results of a certain interest, though they would be of no great value from the point of view of an advance in our theories.

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[1] Caven, *Trans.*, **81**, 1362 (1902).

[2] Janowski, *Monatsh.*, **9**, 831 (1888).

[3] Willstätter and Benz, *Ber.*, **39**, 3492 (1906).

The most important problem in the division of the subject devoted to the double bond is certainly that of the addition of bromine in the trans-position in unsaturated acids, which are attacked in the cis-position by oxidising agents. There seems little doubt that this difference really exists, and from the theoretical point of view it is perhaps the most important of all the present problems of stereochemistry. The first question which must be settled is, of course, that of the exact influence exerted by the nature of the radical or atom which attacks the double bond. In the light of our present knowledge it seems likely that, since the difference is found when a monovalent element like bromine is substituted for a divalent one like oxygen, the divalent element is able to act as a bridge between the valencies of the two carbon atoms, and thus hinder, or encourage, some intramolecular change. Clearly, the problem should be attacked by finding some polyvalent element other than oxygen which is capable of attacking double bonds, and studying the behaviour of this atom with regard to the position in which it adds itself on to the double bond. However the solution of this problem be obtained, it will certainly render clearer the fundamental principles of the subject, for at present we have no hypothesis which makes the known facts at all comprehensible.

Turning for a moment from wider questions, attention may be drawn to the urgent need of new methods by the aid of which the configuration of compounds may be accurately determined. At the present time there are hardly any reliable ones known, even in the case of the ethylene isomers. In the hydrazone series nothing at all has been done in this direction; and the same may be said of cases like that of the quinone oximes. The same lack is felt in the case of the configuration of those open-chain compounds which are not optically active; here, except in a few isolated cases, we know absolutely nothing of the arrangements of the atoms in space. It is unlikely that we have already discovered all the possible means of determining the configuration of all these substances; and a successful research on the subject would well repay any time spent upon it.

There are, however, greater questions than these. For instance, the stability of various polymethylene rings seems to be a matter which is influenced more by space relations than by chemical factors; and a careful study of the cases which are in agreement with Baeyer's Strain Theory and a comparison between them and those instances which are exceptions to the theory might conceivably yield valuable results, and might quite possibly throw light upon the causes of the modification of the stability which is brought about by varying the number of carbon atoms in the ring. From this point of view the almost equal stability of the five- and six-membered ring systems is specially noteworthy, and a special study of the exceptional cases already known to us might be expected to suggest new lines of research on the point.

In the problems hingeing upon steric hindrance, much has yet to be investigated. It is unnecessary to enter into details; one case will suffice as an example. In the foregoing pages it has been shown that the second ring in naphthalene compounds sometimes exercises a hindering influence, while in other reactions this is not observed; the cases of oxime formation, esterification, hydrolysis, and the benzidine change may be recalled. If the hypothesis of steric hindrance, pure and simple, be applied to these instances, we are obviously forced to the conclusion that the second nucleus in the naphthalene molecule changes its configuration according to the character of the nucleus to which it is attached, and on this view we may be able to arrive at interesting results. On the other hand, if we reject the steric view, an equally important series of deductions might be drawn from the same facts, since, if steric considerations do not intervene, then the different effects noticed must be due to changes in the chemical character of the two nuclei.

Another instance of steric hindrance which deserves careful study is that of the phenomena generally grouped under the head of Bischoff's Dynamic Hypothesis. The modern standpoint of chemistry seems to be becoming, on the one hand, more mechanical, but on the other less grossly materialistic than the position of a decade ago; and though we are still

forced to speak of "collisions" between atoms, we use the word more as a convenient nomenclature than as an actual representation of the action. We are thus in danger of letting go one simple conception without having anything more than mere words to take its place; and it seems expedient at the present time to review the whole question in order to bring it into consonance with our present views in other fields of knowledge. It may be that the "collision" idea is the true one, but there is no reason why the whole question should not be studied afresh from a new point of view. It is unlikely that any experimental work carried out in this field after the present time will do more than reaffirm the main points already established by Bischoff; but some new explanation of the occurrence of "critical positions" might lead to results of the greatest importance.

This is not the place to deal with the practical applications of stereochemistry, which have already been fully treated in other works. It is to be anticipated that saccharimetry by the aid of a polariscope is not the last word on the subject.

Up to the present, this branch of chemistry has not been brought much into connection with other sciences, but the possibilities in this direction are to be surmised from the results in the case of the investigation of the origin of petroleum. From the geological point of view it is of the greatest interest to know whether petroleum is an inorganic product or is produced by the degradation of vital organisms. Walden[1] pointed out that if petroleum were an optically active substance, its vital origin was almost a certainty. This activity has been established by Ragusin in the cases of Caucasian and American petroleums, so that the question is now practically beyond doubt.

Finally, it may be well to point out that there seem to be possibilities of fruitful research in connection with the problems of dimorphism. Already some tentative efforts have been made in this direction; for example, Knoevenagel has endeavoured to explain the occurrence of two forms of

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[1] Walden, *Naturwiss. Rundschau*, **15**, 15 (1900).

benzophenone by the aid of his space formula for benzene, but no broad study of the question has yet been attempted. To any one desirous of taking up such a research, the study of O. Lehmann's *Molekular-physik* may be recommended, as in that book he has collected some scores of instances of dimorphism among organic and inorganic compounds.

APPENDIX A.

THE RELATIONS OF STEREOCHEMISTRY TO PHYSIOLOGY.

IT was pointed out in one of the early chapters of this book that while some inorganic compounds possessed the faculty of rotating the plane of polarization of light passing through their crystals, they lost this property when dissolved or powdered; while, on the other hand, certain carbon compounds retain their influence upon the plane of polarization even when fused or dissolved. In the first case, we are dealing with the effect of a mere crystalline form; in the latter case we have a fundamental asymmetry within the molecule itself. Until a few years ago, the only known sources of optically active carbon compounds were natural ones; and for a time the case resembled that of organic chemistry previous to Wohler's synthesis of urea. A section of chemists, even quite recently, maintained that vital action was essential to the production of asymmetric compounds.[1] It seems hardly necessary to point out that this view is based upon a misconception of the problem. It is generally recognized that the synthesis of urea definitely destroyed the hypothesis that so-called organic substances could only be formed by the action of living matter; and yet it is admitted that Wohler himself was a living agent. But the upholders of the vitalistic theory of asymmetric synthesis insist, that because Pasteur employed his hands to separate the crystals of the active tartaric acids, therefore vital influence came into play, and the synthesis was merely another example of the vital method. This style of argument misses the main point altogether. When we speak of the formation of a substance by vital action, we imply its formation *within* some vital organism, not its production in the laboratory by the agency of a human being. The latter method is usually treated as a purely chemical one, though,

[1] See the controversy in vols. **58** and **59** (1898–9) of *Nature*, in which Japp, Bartrum, Errera, Fitzgerald and others took part.

strictly speaking, it is no doubt merely a modification of the other.

But even if we admit this, still the production of asymmetric compounds by the aid of non-vital forces is not rendered impossible, for there are many "non-symmetrical forces" known to us in nature, the action of any one of which might be sufficient to give rise to an asymmetric compound from purely symmetrical materials. The work of Byk[1] has shown that an active body might be produced by the action of natural forces alone, without the interference of life in any form.

The actual processes by means of which living organisms are able to synthesise optically active compounds from purely symmetrical ones have not yet been discovered; we are ignorant even of the broad lines along which the operation proceeds. It is possible that the synthetic processes of the living organism take place very slowly, so that certain natural forces, such as the earth's rotation, or its magnetism, have time to influence the reactions. Experiments on this line might conceivably lead to interesting results.

When we come to consider the stereochemical configuration of living bodies, we find that where there is a possibility of stereoisomerism being shown by a natural product, the vegetable or animal cell generally contains the active form of the compound. The majority of proteids are almost all lævo-compounds, while the bile acids occur in the dextro-configuration. Dipentene appears to be an exception to this rule, as it is found in the racemic form. From the fact that so many of the products of living organisms display optical activity, we may deduce that the organisms themselves have the power of differentiating between the dextro- and lævo-compounds, destroying the one form while leaving the other more or less intact. A considerable amount of research has been carried out on the subject, and, on the whole, it appears to confirm this view. It seems probable that the tissues of living beings are themselves asymmetrical, and, in their action upon foreign bodies, select those whose stereochemical configurations best fit in with their own, while they reject the stereoisomeric types whose configurations appear to be unfavourable to mutual action.

In the following pages a brief account will be given of the results arrived at in some typical cases. It is too early to generalize on this subject, as at present the data at our disposal

[1] *Zeit. physikal. Chem.*, **49**, 641 (1904).

are disconnected, and in some instances contradictory; all that will be attempted will be to show the influence which the stereochemical character of a compound exerts over its action upon living tissues. The relations between fermentation and stereochemistry have been dealt with in another volume of this series,[1] so we need not enter into that question here.

Brion[2] studied the action of the animal organism upon the four tartaric acids. His results may be summarised as follows. Lævo- and meso-tartaric acids seem to be oxidised to an equal extent; dextro-tartaric is destroyed to a less extent than either; while racemic acid is least oxidised of all. This behavour on the part of racemic acid seems to show that it is not decomposed into its components during its passage through the organism.

In the pentose series, Neuberg and Wohlgemuth[3] have examined the case of the three arabinoses and their derivatives. The results obtained when the substances were introduced through the mouth, I., subcutaneously, II., and intravenously, III., agree fairly well. The figures below give the percentage of substance recovered from the urine of rabbits :—

Substance.	I.	II.	III.
l-Arabinose	14·5	7·1	28·3
d- ,, ...	31·2	36·0	31·0
r- ,, ...	28·5	31·7	29·0

The three arabonic acids showed similar differences when they were supplied to the animal in the form of sodium salts: less of the lævo- than of the dextro-variety was attacked in this case. After dextro- or racemic arabite was supplied to the animal, small quantities of pentoses appeared in the urine. This was not found when lævo-arabite was used. In the case of the human organism an even greater resolution of racemic arabinose took place, two-thirds of the excreted substance being the active form. From this the authors draw the deduction that the formation of racemic arabinose which occurs in the human body in certain diseases must take place in some organ so situated that after being liberated from it the arabinose is not submitted to any process of resolution. Nagano[1] finds that lævo-xylose is better absorbed than lævo-arabinose.

[1] Mellor, *Chemical Statics and Dynamics*.

[2] Brion, *Zeit. physiol. Chem.*, **25**, 283 (1898).

[3] Neuberg and Wohlgemuth, *Ber.*, **34**, 1745 (1901); *Zeit. physiol. Chem*, **35**, 41 (1902).

[1] Nagano, *Pfluger's Archiv*, **90**, 389 (1902).

Neuberg and Mayer[1] have studied the case of the three mannoses. Here, again, the dextro-variety seemed best fitted for nourishment. It was noticed that during the passage of the three compounds through the system each of them was to some extent converted into a derivative of the glucose series. This is of interest, since it shows that the physiological processes can produce a change in the configuration of sugar molecules. Rosenfeld[2] found that sugars are excreted in urine in the following order: galactose, mannose, dextrose; the alcohols also in the order, dulcite, mannite, sorbite.

These instances are sufficient to show that the configuration of the compounds has considerable influence upon their physiological action. We may now give an example of stereochemical influences upon the senses of taste and smell. In passing, it is interesting to note that Pasteur considered nerves as asymmetric organisms.

Piutti[3] states that dextro-asparagine has a sweet taste, while the lævo-isomer is insipid. This difference is not found in the asparagine derivatives, for *d*- and *l*-aspartic acid have the same taste. In the case of glutaminic acid, Menozzi and Appiani[4] found that the dextro-form had a sweet taste, while the lævo-form was tasteless. Sternberg[5] states, that as a rule there is possibly a quantitative but not a qualitative difference between the effects of stereoisomers upon the sense organ. A disputed case is that of mannose and glucose. W. A. van Ekenstein[6] states that the former tastes sweet, while the latter is bitter. This has been contradicted by Neuberg and Mayer.[7] Werner and Conrad[8] found a difference between the odours of the methyl esters of the two active trans-hexahydro-terephthalic acids; while Schmidt and Tiemann observed that racemic terpenes frequently were less strongly odoriferous than the active isomers.

The toxic qualities of two stereoisomers have, in some instances, been found to be different, and, in others, identical.

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[1] Neuberg and Mayer, *Zeit. physiol. Chem.*, **37**, 530 (1903).
[2] Rosenfeld, *Centralblatt f. innere Medicin*, **21**, 177 (1900).
[3] Piutti, *Compt. rend.*, **103**, 134 (1886).
[4] Menozzi and Appiani, *Atti R. Accad. Lincei*, [5], **2**, II., 421 (1893); *Gazzetta*, **17**, 126, 182 (1887).
[5] Sternberg, *Archiv. Anat. Phys.*, **1898**, 457.
[6] Van Ekenstein, *Rec. trav. chim.*, **15**, 222 (1896).
[7] Neuberg and Mayer, *Zeit. physiol. Chem.*, **37**, 545 (1903).
[8] Werner and Conrad, *Ber.*, **32**, 3052 (1899).

Chabrié's results with the tartaric acids[1] are stated by Cushny[2] to be valueless, as the toxic medium in this case is the hydrogen ion. Ladenburg and Falck[3] compared the action of active dextro-coniine and the synthetic alkaloid, but found no difference between the two. Poulsson[4] studied the action of the cocaines on the tongue, and found that the paralysing action of dextro-cocaine was stronger, and set in more rapidly than that of lævo-cocaine, but the effect was not so lasting as in the case of the lævo-isomer. The fatal doses seem to be the same for each isomer in the case of frogs or rabbits. This difference in action was confirmed by Ehrlich and Einhorn.[5] The therapeutic action of atroscine is said to differ from that of scopolamine.[6] Cushny[7] found that atropine and hyoscyamine act in the same way and with equal potency on the central nervous system in mammals. Atropine possesses a more powerful stimulant action on the reflexes of the spinal cord than hyoscyamine. On the other hand, hyoscyamine is almost twice as powerful as atropine in its action on the nerve ends of the salivary glands, the heart, and the pupil. Now, atropine is racemic hyoscyamine; and the other base used was lævo-hyoscyamine: so that we have the following results: *dl*-hyoscyamine has the same effect as *l*-hyoscyamine on the central nervous system of mammals. Therefore, in this case, the actions of *d*-hyoscyamine and *l*-hyoscyamine must be identical. On the other hand, *dl*-hyoscyamine has a more powerful action on the spinal cord than *l*-hyoscyamine has; so that in this case the *d*-isomer is the more effective. In the case of the effects on the pupil nerve endings, since *l*-hyoscyamine is almost twice as powerful as *dl*-hyoscyamine, it seems probable that *d*-hyoscyamine is almost without action.

Albertoni[8] finds that cinchonine, which is dextro-rotatory, differs from its lævo-rotatory isomer cinchonidine. The latter acts much more slowly, and requires larger doses to produce the same effect; it produces vomiting, and has a very strongly marked tendency to cause spasms.

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1 Chabrié, *Compt. rend.*, **116**, 1410 (1893).
2 Cushny, *J. Physiol.*, **30**, 193 (1904).
3 Ladenburg and Falck, *Annalen*, **247**, 83 (1888).
4 Poulsson, *Archiv. exp. Path. Pharmak.*, **27**, 309 (1890).
5 Ehrlich and Einhorn, *Ber.*, **27**, 1870 (1894)
6 Hesse, *J. pr. Chem.*, [2] **64**, 353 (1901).
7 Cushny, *J. Physiol.*, **30**, 193 (1904).
8 Albertoni, *Archiv. exp. Path. Pharmak.*, **15**, 272.

The two isomers, quinine and quinidine, also differ in physiological action, as the second has no narcotic properties, although it shares the febrifugial action of quinine.[1]

Mayor[2] found that dextro- and lævo-nicotine were different in physiological properties, the latter being twice as poisonous as the former. When lævo-nicotine is injected, it produces pain and excitation; under the same conditions, dextro-nicotine seems painless. The former causes paralysis, spasms, retardation of the heart's action, and finally death by cessation of respiration; dextro-nicotine, on the contrary, produces only a strong shivering fit, which soon passes.

It seems that the stable isomer has usually less action than the labile form. This has been shown above in the cases of atropine and its derivatives, and another example is furnished by the stable and labile forms of methylmorphimethine, the former having a much weaker action than the latter.

Hildebrandt,[3] however, examined the ethyl, propyl, butyl, and isoamyl derivatives of benzyl-coninium iodide, and found that the isomer having the lower melting-point had a less intense action than the other.

We have now brought forward sufficient evidence that physiological action and configuration are closely related in the case of asymmetric carbon compounds, and in the following paragraphs it will be demonstrated that changes in the arrangements of atoms in space in other compounds also give rise to differences in physiological action.

Crum Brown and Fraser[4] showed that when certain alkaloids were allowed to unite with methyl iodide, they gained a new physiological property without losing any of their previous efficiency. This new attribute resembles the chief property of curare, in that the methyl iodide addition products have a paralysing action upon the ends of the motor nerves of muscles; and it has recently been shown by Boehm[5] that when curine (the tertiary base contained in curare) is treated with methyl iodide it gives curarine, a substance two hundred and twenty-six times as poisonous as the mother substance, and

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[1] Macchiavelli, *Jahresbericht d. Chemie*, **1875**, 772.

[2] Mayor, *Ber.*, **37**, 1225 (1904).

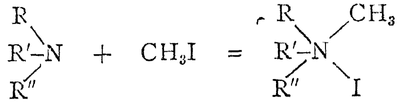
[3] Hildebrandt, *Ber.*, **38**, 597 (1905).

[4] Crum Brown and Fraser, *Trans. Roy. Soc. Edin.*, **25**, 707 (1868); *Proc. Roy. Soc. Edin.*, **1869**, 560.

[5] Boehm, *Archiv. d. Pharmacie*, **235**, 660 (1897); *Archiv. exp. Path. Pharmak.*, **6**, 101.

possessing in an acute degree the paralysing properties of curare.

Now, in all these cases we are converting a tertiary base into an ammonium salt, the reaction being expressed by the equation :—

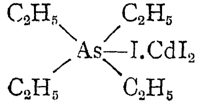


and it seems an inevitable conclusion that it is the change from the trivalent to the pentavalent condition of the nitrogen atom which has conferred the property of paralytic action on the substance. The question is not completely settled by this assumption, however, for we must ascertain whether the new property comes into being in consequence of a change in the nitrogen atom or in the space relations of the molecule. Fortunately, this is easily decided. All that we need do is to replace the nitrogen atom by some other atoms which have faculty of changing from the trivalent to the pentavalent condition. As is well known, compounds of trivalent phosphorus, arsenic, or antimony, derived from the hydrides PH_3, AsH_3, and SbH_3, by the substitution of alkyl groups for hydrogen atoms, have the faculty of combining with alkyl iodides to form salts of phosphonium, arsonium, or stibonium bases of the types :—

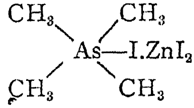
$$P.R_4.I \qquad As.H_4.I \qquad Sb.R_4.I$$

and Vulpian[1] has shown that substances of this type do not show the ordinary physiological behaviour of phosphorus, arsenic, or antimony, but, on the contrary, have a strong curare-like action. The substances actually used by Vulpian were tetra-ethyl-arsonium cadmium iodide, (I.), tetramethyl-arsonium zinc iodide, (II.), methyl-triethyl-stibonium hydroxide, (III.), and tetra-ethyl-phosphonium iodide, (IV.).

(I.)

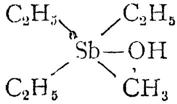


(II.)

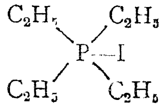


[1] Vulpian, *Arch. de phys. norm. et. pathol.*, **1**, 472.

(III.)



(IV.)



These results go to show that the curare effect is not produced by the actual presence of any given radicals, but rather by the change in stereochemical configuration brought about by the employment of the two secondary valencies of the nitrogen atom. In the section devoted to the stereochemistry of the nitrogen compounds it was shown that in all probability compounds of the type N.*abc* have a plane configuration, *i.e.* all four atoms lie in one plane; while compounds of the type N.*abcdX* have a different disposition of their atoms in space, so that the curare action appears to be due to the change from a plane to a three-dimensional arrangement of the atoms. Most conclusive evidence in favour of the stereochemical explanation is furnished by the behaviour of the sulphur compounds. Since sulphur is a divalent element in the sulphides, it is obvious that the configuration of these compounds must be plane, as a plane can be drawn through any three points. But when alkyl iodides are combined with the sulphides, the configuration of the new compounds is not a plane one, for they may exist in optically active forms. Now, this change from the plane to the solid configuration is accompanied by a change in physiological properties similar to that shown in analogous circumstances by the nitrogen compounds, for it has been observed by Curci [1] and Kunkel [2] that sulphine bases such as trimethyl-sulphine hydroxide, $(CH_3)_3.S.OH$, have a pronounced curare character. An analogous, though not so valuable, case is that of the conversion of a monovalent iodine atom into a tertiary one; alkyl iodides have no marked curare action, but, as Gottlieb [3] has shown, diphenyl-iodonium chloride, $(C_6H_5)_2.I.Cl$, possesses that peculiar paralysing effect on the motor nerves which is characteristic of curare. Here the four groups in the molecule are probably tetrahedrally arranged in space.

The case of the ammonia derivatives of cobalt, chromium, and rhodium has been studied by Bock,[4] who proved that the

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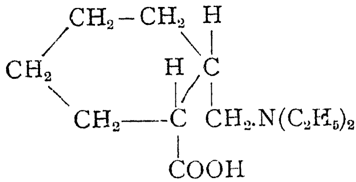
[1] Curci, *Arch. de Pharm. et de Therap.*, 4, 1896.
[2] Kunkel, *Lehrbuch der Toxikologie* (1901).
[3] Gottlieb, *Ber.*, **27**, 1592 (1894).
[4] Bock, *Arch. exp. Path. Pharmak.*, **52**, 1, 30 (1904).

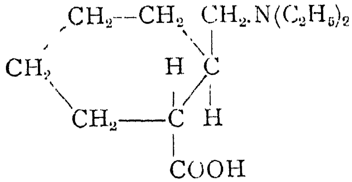
metallic element present in the substance had less influence upon the physiological action than was exerted by the general type of the compound.

The influence which cis-trans isomerism in cyclic compounds can exert on the physiological behaviour of the isomers is exemplified in the case of two acids whose formulæ are given below. The cis-isomer in each case has a stupefying odour, while the trans-compound is devoid of smell :—

Hexahydro-*o*-diethyl-benzylamine carboxylic acids.

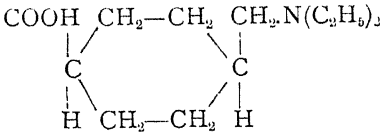


Cis-form, stupefying.

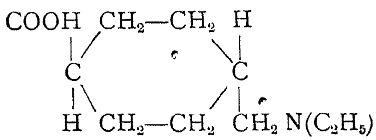


Trans-form, odourless.

Hexahydro-*p*-diethyl-benzylamine carboxylic acids.



Cis-form, stupefying.



Trans-form, odourless.

Not very many facts are known with regard to the differences between the physiological behaviour of two stereoisomers of the ethylene type. Ishizuka[1] found that maleic acid was a much stronger poison than its stereoisomer, fumaric acid; 1·94 grammes for every kilogramme in a dog's weight was a fatal dose of the former acid, while the same dose of fumaric acid was harmless. It is probable that this difference is due to the greater affinity constant of maleic acid. The same toxic effects are noticeable in the case of the cultivation of *Penicillium glaucum* in solutions of the two acids: the fungus grows readily in fumaric acid, but only very slowly in a maleic acid solution. Kahlenberg and True,[2] using *Lupinus albus L.*, were able to establish the following figures. Fumaric acid solution containing one gramme molecule in 6400 litres was fatal; on dilution to 12,800 litres, the organisms were not destroyed. One gramme molecule of maleic acid in 3200 litres was fatal; but on dilution to 6400 litres the solutions had no toxic action. These results, being the converse of those obtained with *Penicillium glaucum*, seem to point to a difference in the molecular configuration of the fungus used. Some further research in this field might lead to interesting results, as the case may eventually prove to be parallel to the action of ferments on the sugars.

The influence of geometrical isomerism upon taste has been observed in one or two cases. In the ethylene series we have the example of benzyl-β-amidocrotonic ester, one form of which (m.p. 79–80°) is quite tasteless, while the isomeric compound (m.p. 21°) has an intensely sweet taste, which resembles that of peppermint. A similar difference is shown among the geometrically isomeric carbon-nitrogen compounds, for the syn-form of anisaldoxime is tasteless, while the ordinary anti-form is very sweet.

In the body of this volume it was mentioned that Ladenburg's explanation of isomerism in the case of compounds in which a nitrogen atom forms part of the ring had been applied to tropine and ψ-tropine. The following paragraphs contain a summary of evidence from the physiological side of the question which appears to render Ladenburg's view doubtful.

Tropine and ψ-tropine are isomeric substances having the common structural formula:—

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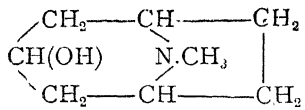
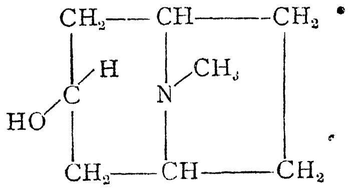
1 Ishizuka, *Bull. Coll. Agr. Tokyo*, **2**, 484 (1897).

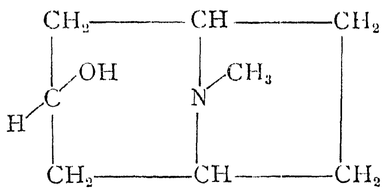
2 Kahlenberg and True, *Botanical Gazette*, Chicago, **22**, 181 (1896)



The mandelic acid derivative of tropine has a strong mydriatic action, while the analogous ψ-tropine derivative is inactive. If we reject the Ladenburg hypothesis of the unsymmetrical arrangement of the nitrogen valencies in space, on which view the isomers are represented by A and B :—

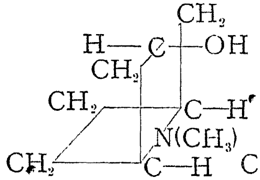


A

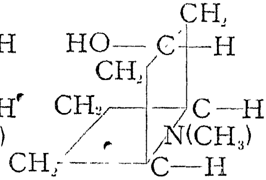


B

we are driven to accept the only alternative hypothesis, viz. to attribute the isomerism to differences in the space arrangement of the atoms in the group –CH(OH)–. If a model be built up from the structural formula, it will be found that the two rings in the molecule lie at an angle to one another, instead of being in the same plane, so that a rough diagrammatic representation of the model would resemble one of the figures below :—



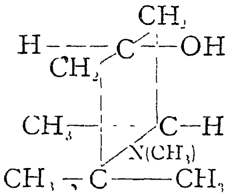
(I)



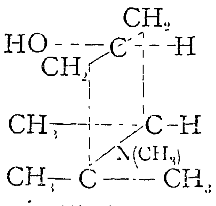
(II)

The difference between the two formulæ, as can be seen by inspection, lies in the fact that in formula (I.) the hydroxyl group lies on the same side of the molecule as the two hydrogen atoms, while in formula (II.) it lies on the opposite side of the molecule, adjacent to the methylene groups of the ring.

The compound N-methylvinyl-diacetone-alkamine can also exist in two stereoisomeric forms, which are represented by the two figures :—



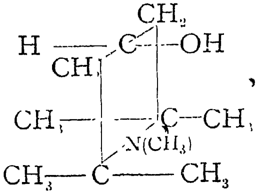
(IA.)

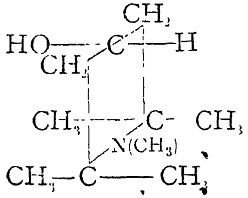


(IIA.)

It is plain that formulæ (I.) and (IA.) are analogous to each other, while (II.) and IIA.) are also alike.

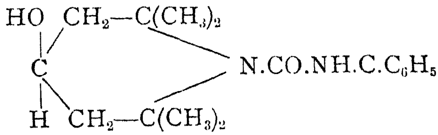
Now, one of these N-methylvinyl-diacetone-alkamines, either (IA.) or (IIA.), has the same physiological action as tropine, while the other is inactive, like ψ-tropine. The resemblance between the two series is thus very close. The chief difference between the formulæ (IA.) and (IIA.) seems to be that in the first case the hydrogen atom on the bridge lies on the same side of the molecule as the two methyl groups, while in (IIA.) it lies on the side adjacent to a hydrogen atom. If we could replace this hydrogen atom by a methyl group, we should destroy the possibility of a stereoisomerism. Not only so, but from the physiological action of the new compound we should be able to draw conclusions as to the effect of the hydroxyl radical lying on the same side of the molecule as two methyl groups, for in the new substance it must be adjacent to two methyl groups in any case, as the two configurations are identical :—





This compound is actually known, being N-methyl-triacetone-alkamine. An examination of its properties shows that it has the same physiological effect as tropine. From this we may deduce that the physiologically active N-methylvinyl-diacetone-alkamine has the configuration (IIA.), and that therefore tropine must have the space formula (II.), while ψ-tropine is (I.).*

In the case of tropine and N-methylvinyl-diacetone-alkamine it is the labile isomer which has a physiological effect; the stable isomer being inactive. From analogy, then, we should expect the physiologically active N-methyl-triacetone-alkamine to be a labile compound, if the Ladenburg hypothesis were correct; but as so far no isomer of it has been isolated, it appears to be a stable body. This fact does not affect the question from the point of view of the alternative theory of the isomerism, but from the Ladenburg point of view it is very serious. It should not be overlooked, however, that Groschuff[1] mentions two isomeric compounds of the formula :—



a case which only the Ladenburg hypothesis can explain. It would be interesting to know the physiological actions of these two substances.

The differences in physiological action which are observed in the cases of cocaine, eucaine, and α-cocaine may possibly be due to spacial influences, but nothing is at present known on the point.

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* This is, of course, not a proof of the *absolute* configuration of the compounds, for opposite results are obtained by choosing as a starting-point the relations of the hydrogen atom to the methyl groups. If this were done, tropine would be represented by (I.) and ψ-tropine by (II.).

[1] Groschuff, *Ber.*, **34**, 2974 (1901).

APPENDIX B.

DIRECTIONS FOR THE CONSTRUCTION OF STEREO-CHEMICAL MODELS.

CARDBOARD tetrahedra may be obtained from the firm of Franz Hugershoff, Carolinen Strasse 13, Leipzig.[1] They are mounted on wire stands, and cost about a shilling each. Without the stand, they cost threepence each. These tetrahedra can be obtained in two forms, either of the usual type, or with truncated points; the latter form is suitable for making models in which two or three tetrahedra are joined rogether.

Wooden tetrahedra, suitable for private study or for class-room demonstration, have been designed by A. Eiloart, and may be obtained from Messrs. Baird and Tatlock, Cross Street, Covent Garden, London. A set of six tetrahedra, forty tin caps with the formulæ of various radicals painted upon them, and a series of pins for joining the tetrahedra together, costs £2 12*s*. 6*d*. Stands to fit these models can be had from the same firm for 6*s*. 6*d*.

The Austro-American India-rubber Manufacturing Company, Hütteldorfer Strasse 74, Breitensee, Vienna, Austria, sell rubber models in which four tubes branch from the centre of the model in the directions of the four corners of a tetrahedron. These models cost thirty shillings per hundred; oxygen, nitrogen, and hydrogen atom models to match cost respectively twenty, fifteen, and six shillings per hundred. Messrs. Baird and Tatlock make similar models at eighteenpence the set, each set being sufficient to illustrate the isomerism of the tartaric acids. More complete sets, containing models of twelve carbon atoms, cost nine shillings. A larger size of model may be obtained at double the price.

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[1] H. Wislicenus, *Zeit. Angew. Chem.*, **15**, 49 (1902).

Engler's models are also sold by Messrs. Baird and Tatlock at twenty-two shillings per set. They are balls connected by flexible tubing.

The most convenient set of models [1] is that supplied by the firm of C. Desaga, of Heidelberg, at a cost of five marks, postage one and fourpence extra. For this, the following are supplied. Eight large balls, representing carbon atoms; four others, representing nitrogen atoms; two smaller balls, representing oxygen atoms; thirty small balls, which represent any mono-valent atoms or radicals. All these are bored so that they can be joined together with lead rods, which are supplied to represent bonds. The models are enclosed in a neat wooden box. This set is quite sufficient for most purposes, and the models are of a most convenient size.

It is, however, quite easy to make a number of models for studying stereochemical problems; and in most cases it is best to do this one's self, as there are many models which cannot be bought ready made.

The simplest method of making tetrahedra is to cut them out of yellow soap. Plasticine may be used instead of soap, but it does not appear to be so satisfactory. Needles make the best bonds for models of this type.

Models may also be made from cork. It is not necessary to cut the cork into shape; four matches or pins are thrust into the cork at the proper angles, and a tetrahedral arrangement is thus obtained. These models may be joined together by slipping pieces of small-bore rubber or lead tubing over the ends of the two pins which are to be united.

Tetrahedra may be cast in any easily melted material, such as sealing-wax, moulds being made from tin or cardboard, and moistened to prevent sticking. Knoevenagel [2] recommends a mixture of one part of turpentine, one part of shellac, and one and a half parts of precipitated calcium carbonate. This makes rather too stiff a mixture for casting, but the proportions may be varied to produce the desired consistency.

Cardboard tetrahedra are made by cutting the cardboard into the shape of the figure below (Fig. 82), folding it along the dotted lines, and fastening the parts marked *aa'*, *bb*, and *cc'* together with paste or gum, *a*, *b*, and *c* being kept inside the tetrahedron. The three points marked *d* come together, and should be made secure with a little sealing-wax:—

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[1] Jacobson, *Chem. Zeit.*, **16**, 808 (1892).

[2] Knoevenagel, *Annalen*, **311**, 201 (1900).

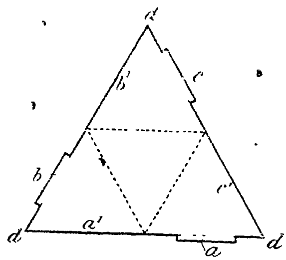

FIG. 82.

This arrangement produces the ordinary sharp-pointed tetrahedra, but as in some cases these are unsuitable, directions for making truncated ones may be given. The cardboard should be cut into the shape below (Fig. 83), folded at the dotted lines, and then a joined to a', etc., as in the last case. This will produce an incomplete tetrahedron whose four empty corners must be filled in by pieces the shape of the smaller figure, the flaps z being gummed inside the tetrahedron.

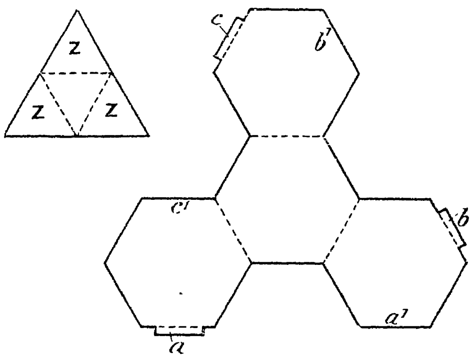

FIG. 83.

Wooden tetrahedra can be obtained from any carpenter. They should have holes bored in each apex, in the centre of each face and edge, of a size to fit the metal rods or wires used to join them together. It is well to have brass tubes sunk in these holes, as this prevents any splitting of the wood when strain is applied to the wires. The most convenient size for the tetrahedra is about four inches measured along the edge.

We must now consider the construction of various benzene models.

Græbe's model (p. 505) is obtained by linking the six carbon atoms together in the way shown in the illustrations.

Marsh's model (p. 506) is readily made by drawing a hexagon upon paper, dividing it into equilateral triangles, and placing a tetrahedron upon each triangle.

Vaubel's formula (p. 516) is most easily constructed from cardboard tetrahedra. As in the Marsh formula, a hexagon is first drawn; but instead of the tetrahedra being placed on one side of the card on which it is sketched, they are placed alternately above and below it. They can be secured with gum. When wooden tetrahedra are used, the linking must be done in such a way as to produce the required figure, the tetrahedra being joined edge to edge.

Sachse's formula (p. 518) is best put together in two steps. In the first place, the carbon atoms are attached to each other in two groups of three. It is best to use wires fixed along the edge of cardboard tetrahedra from A to B, B to C, and C to A (Fig. 84). One piece of wire should be used, if possible; it may be fixed to the edges of the tetrahedra by means of sealing-wax, or by pasting a piece of paper over the top of it.

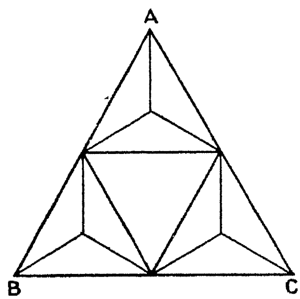

FIG. 84.

We have now got the two groups, each containing three tetrahedra; and all that is necessary is to fix them together with wires or sealing-wax.

Collie's benzene model (p. 523) may be bought from Messrs. Baird and Tatlock at a cost of fifty shillings. Directions for making it are unnecessary, as the illustrations given are sufficient. The tetrahedra may be of wood or

of cardboard, with cork cores; rubber tubes represent the bonds, which are attached to the carbon atoms by means of small rings and hooks, such as are used on model yachts. Each carbon atom must be free to revolve around its support. For small models, thin elastic represents the bonds better than rubber tubing, which is not sufficiently extensible.

Models of the two configurations of hexamethylene have been devised by Sachse,[1] and are constructed in the following manner. To make the first, a piece of cardboard is cut into the shape shown in Fig. 85: six tetrahedra of a suitable size are placed upon the six shaded triangles; and, after the card has been folded along the lines BC, CD, DE, EF, and FG, AB and GH are joined together.

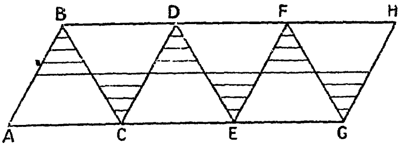

FIG. 85

The same configuration is obtained by using a piece of cardboard of the shape shown in Fig. 86. Tetrahedra are attached to the numbered triangles, those on 1, 3, and 5 being on one side of the card, while those attached to 2, 3, and 6 are on the other side.

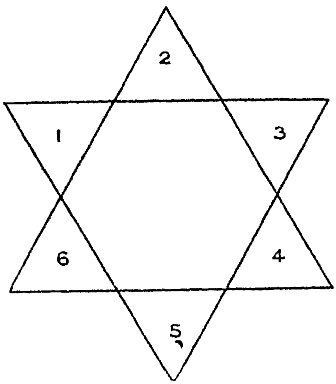

FIG 86

[1] Sachse, *Ber.*, 23, 1363 (1890).

The other configuration is slightly more complicated. Two pieces of cardboard are required, which must be cut into the shapes shown in Figure 87. Tetrahedra are next affixed to the shaded parts, as before, and the two pieces are joined

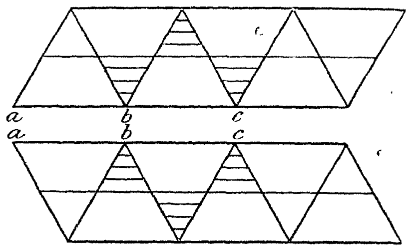

FIG. 87.

together in such a way that similar letters come together; *i.e.* *a* to *a*, *b* to *b*, etc. The clearness of these models is greatly increased if all the parts except the tetrahedra be blackened with Indian ink.

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M

THE END